DRUG LAG

HEARING

BEFORE THE

SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT

OF THE

COMMITTEE ON SCIENCE AND TECHNOLOGY U.S. HOUSE OF REPRESENTATIVES

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DRUG LAG

WEDNESDAY, SEPTEMBER 16, 1981

U.S. HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
SUBCOMMITTEE ON NATURAL RESOURCES,
AGRICULTURE RESEARCH AND ENVIRONMENT,
Washington, D.C.

The subcommittee met at 9:35 a.m., in room 2318, Rayburn House Office Building, Hon. James H. Scheuer (chairman of the subcommittee) presiding.

Present: Representatives Brown, Carney, Sensenbrenner, and Schneider.

Staff present: Jonah Shacknai.

[A statement from Congressman George E. Brown, Jr., follows:]

STATEMENT OF HON. GEORGE BROWN

Mr. Chairman, it is my great pleasure to be here this morning as our subcommittee continues its important investigation of the drug approval process in the U.S. As you know, this is a subject which has been of great interest to me for several years, and the Science, Research and Technology Subcommittee which I formerly chaired had itself conducted hearings on the drug lag.

It is my privilege this morning to introduce Michelle and Henry Gackstetter, two fellow Southern Californians. They, along with Mrs. Carol Gackstetter, have displayed enormous courage in the fight against SSPE, which has afflicted Michelle for the last decade. SSPE is a rare, neurologically degenerative disease which affects about 200 children each year in the U.S. It is believed to be caused by a measles-like virus infection and until very recently has always been fatal.

Michelle, along with a handful of other young people, has been treated with Isoprinosine, a drug manufactured by the small Californian firm of Newport Pharmaceuticals. Although approved in 47 other countries including Canada, Israel and Japan, the drug remains unapproved by the F.D.A. Doctors at the most prestigious medical institutions in the world have heralded Isoprinosine as the only effective treatment of the dreaded SSPE—yet it remains unavailable in the U.S.

The experience of the Gackstetter underscores the need for reform of the drug approval process. I join with you, Mr. Chairman, in welcoming them before our subcommittee to tell their story.

Mr. SCHEUER. The Subcommittee on Natural Resources and Agriculture Research and Environment will come to order.

Today's hearing will be a continuation of our investigation of the so-called drug lag, the delay in the drug-approval process in the United States.

This began about 4¼ years ago, as a matter of fact in May 1977, when, as chairman of the Oversight Committee of the Science and Technology Committee I first requested the General Accounting Office to look into the drug-approval process of the Food and Drug Administration. I was concerned at that time at the delays in the process, the general concern in the pharmaceutical industry and

the universities, how far behind we were in the sophisticated, expeditious approval of a new drug. We were behind developments in other parts of the world.

I met with Elmer Staats, then the Comptroller General of the United States and requested him to look into it. And I think he and I thought it would be 1 month or 6 weeks and they'd have three or four people working on it. As it worked out, they spent 3 solid years, and had up to 30 or 40 of their top professional personnel traveling around the world interviewing drug-approval agencies. They worked extensively with the Food and Drug Administration. And I will say to the credit of the Food and Drug Administration leadership, they had extensive and full cooperation of the Food and Drug Administration for that 3-year scrutiny.

They went into all aspects of the drug fraternity in this country, the medical professionals, the universities, the pharmaceutical houses and the medical fraternity itself, the AMA, and the various State and county medical societies. They spent over $1 million in 3 years, with 40 or 50 personnel working solidly around the clock, and produced a very major report, and a subsequent followup report which you will hear discussed this morning.

At any rate, their reports and our investigations have confirmed my suspicions held in 1977, that there was a serious lag in the drug-approval process, and that the Food and Drug Administration, through a combination of factors, had, to a very real extent, made our American citizens, 220 million of them, second-class patients, certainly compared to citizens in developed countries all around the world.

Delays of 7 to 10 years in the drug-approval process, costs of up to $70 million for approving a new drug, meant, first, that the pharmaceutical companies had enormous time and dollar barriers, didn't undertake to do many drug with small constituencies that they would have undertaken had the approval process been less horrendously burdensome. And, second, it meant that the American people for years were denied life saving and life enhancing drugs that citizens all over the world were using and benefiting from.

Tens of thousands of patients each year in our country have died, and hundreds of thousands, if not millions, have suffered needless discomfort, pain, and suffering because of the unavailability of the most cost-effective kind of health care; namely, drug therapy.

American doctors have been limited to a smaller selection of medicines with which to treat individual needs of their patients than doctors around the world, patients here who are suffering life threatening and extremely debilitating diseases.

And, indeed, many Americans have been forced to go overseas to receive their medical treatment, to England, France, Germany, or Japan to obtain drugs that they could not obtain in the United States. So one might say very accurately, and somewhat tragically, that there is no drug lag in the United States for the rich, for the people who can afford to go overseas to escape the dead hand of the FDA in making drugs unavailable here that people who have the capacity and finances to travel can find overseas.

Another problem that is of concern to all of us is the evidence of declining American innovation in the pharmaceutical industry.

Statistics tells us that the posture of the U.S. companies in relationship to their counterparts in western Europe and Japan has been deteriorating consistantly since 1965. The annual growth in R. & D. in the United States from 1973 to 1979 was about 11 percent. It was double this figure or more in West Germany, England, and Japan, double the rate of pharmaceutical innovation.

Ten years ago, American drug companies were performing approximately 2 percent of their pharmaceutical research and development overseas. Today, in great measure because of the dead head of bureaucracy in the FDA, they're doing 20 percent, 10 times the percent, of their R. & D. abroad. That means we are exporting capital, we're exporting talent, and we're exporting the availability of lifesaving drugs that are not available here for many, many years.

I might also say I was in Japan for 2½ weeks in the last 30 days. It's perfectly clear that if we don't get our act together in terms of rapid approval of pharmaceutical drugs that the Japanese are gearing up to make a massive impact in this area in global trade that will not only decimate us in terms of sales of pharmaceutical drugs throughout the world but will impact the market in this country, and will have a devastating effect on pharmaceutical sales of American companies in America.

Today's hearing presents the committee with a splendid example to learn what the FDA has done, what it's planning to do, and sharpen our insights into the so-called drug lag. The General Accounting Office will present its latest findings on the success and the failures of several FDA issues, and the new Commissioner of the FDA, Mr. Hayes, will then describe the Reagan administration's plan for reform of the drug approval process.

Let me say, incidentally, in this regard, that I have met several times with the Commissioner, with Vice President Bush, and I'm enormously encouraged at their acceptance of the challenge to make the R. & D. process and the NDA process, the investigation of new drug process, and the new drug application process, more responsive to the needs of the American people and American patients.

I'm confident that Dr. Hayes this morning will reflect that concern. I thank him in advance for his kindness in being willing to appear before us.

To start off the morning, we're going to hear from a very fine, attractive, courageous, intelligent young lady and her father, Michele and Henry Gackstetter. They will describe, along with their physician, Dr. Paul Dyken, the struggle they have had against a rare degenerative disease called SSPE. They will translate that into the King's English.

To introduce them, let me now recognize our distinguished and very hard working contributing ranking minority member, Congressman Bill Carney.

[The prepared statement of Mr. Scheuer follows:]

OPENING REMARKS OF CHAIRMAN JAMES H. SCHEUER

The Subcommittee on Natural Resources Agriculture Research and Environment will come to order.

Today our Committee continues its investigation of the drug approval process in the United States.

Our investigation began over 4 years ago, when, as Chairman of the Oversight Subcommittee, I requested the General Accounting Office to Conduct a review of how new and important drugs are approved.

The results of their study, released in 1980, confirmed my worst suspicions—that the U.S. lagged behind the rest of the medically advanced world in making new medications available to suffering patients.

In other words, the FDA, which is charged with safeguarding the health of the public, has in fact caused Americans to become second class patients.

The substantial delays of 7–10 years and the exhorbitant cost of up to $70 million of getting a new drug onto the market have produced no net benefits in terms of safer, more effective drugs.

On the contrary, tens of thousands of patients have paid a very high price because of the unavailability of one of the most cost-effective methods of health care—drug therapy.

American doctors have been limited to a smaller selection of medicines from which to treat the individual needs of their patients, many of whom suffer life-threatening or extremely debilitating illinesses.

Many American Patients have actually been forced to go abroad—to England, Canada, Germany or Japan—to obtain drugs that they are deprived of in the U.S.

Another matter of great concern is evidence of declining American innovation in the pharmaceutical industry.

Statistics indicte that the posture of U.S. companies relative to their Western European and Japanese competitors has been deteriorating steadily since 1965.

The annual growth rate for R. & D. in the U.S. from 1973 to 1979 was 11 percent.

In England it was 25 percent; in West Germany 20 percent; and in Japan 22 percent.

This is disturbing indeed when one considers that sales and production in the pharmaceutical industry depend vitally on innovation made possible through R. & D.

Today's hearing presents the Committee with an opportunity to learn what the FDA has done, and is planning to do, about the drug lag.

The GAO will present its latest findings on the success and failures of several FDA initiatives.

Commissioner Hayes will then describe the Reagan administration's plan for reform of the approval process.

Let me say in this regard that after meeting privately with the Commissioner and with Vice President Bush, I am enormously encouraged at their acceptance of the challenge to make the IND and NDA process more responsive to the needs of American patients.

I am confident that Dr. Hayes' testimony this morning will reflect that concern.

We will first hear, however, from a very courageous young lady and her father, Michelle and Henry Gackstetter.

They will describe, along with their physician, Dr. Paul Dyken, the struggle they have had against the rare, degenerative disease SSPE.

Let me now recognize our distinguished Ranking Minority Member and my good friend and colleague from New York, William Carney.

Mr. CARNEY. Thank you very much, Mr. Chairman.

If I may, I would like, just for a moment to make a few brief opening remarks, and then I will yield to our colleague from California for the privilege of introducing our witnesses.

I would like to compliment you for holding the hearings, as the problem of drug lag is a serious and continuing one. Your leadership in raising this issue and in addressing the difficulties of the medical community and the pharmaceutical industry in bringing vital new drugs to the marketplace represents the highest use of the congressional hearing process.

Only by bringing these problems to the attention of the public and the Congress can we expect to identify solutions, and only by following through on these problems, as you have done, can we hope to see these solutions implemented. You are to be commended for your continuing leadership on this matter.

I believe that changes are needed in the way this nation develops new drugs and approves them for public use. The question, however, is one of balance: How much emphasis shall we place on the need to speed up the drug approval process versus the need to assure that new drugs are safe before they are brought to market?

This question goes to the heart of the issue of how much regulation is enough, and how much is too much or not enough? It is an issue that concerns us not only with respect to drug approval and usage, but in many other areas of Government as well. For this reason I applaud the efforts of the administration in setting up the Regulatory Review Task Force under Vice President Bush. In no area does the need for regulatory reform cry out as it does in the drug approval process, or present as great a potential for direct, personal benefit to so many people.

Returning for a moment to some of the specifics of the drug review problem, I note that the GAO report mentioned by the Chairman contains two statements I find of particular interest. One of them is that "none of the changes being considered by FDA will revolutionize the drug review process nor are they expected to cause a dramatic decrease in the time required for new drug review." If that is the case, I wonder what has been accomplished so far.

The other statement is that "GAO believes FDA should develop a system to measure its progress in reducing drug review time." I am surprised that this has not been done long ago, and hope that our distinguished witness from the FDA will address this point.

Mr. Chairman, as we begin the hearing, I would like to welcome Mr. Henry Gackstetter and his daughter Shelly, sitting behind us, who will be testifying today of their own personal experience. I hope that the committee will take heed of their words, will review their point of view, and seriously consider the point of view that they bring to you today.

It's absolutely essential not only that they have support, but that the support they receive from this committee will be translated into assistance that will both save lives and improve the quality of life for a large number of American citizens. And to that end we will all work.

And, with that, I thank you very much for the opportunity to be here this morning.

[The opening statement of Mr. Carney follows:]

OPENING STATEMENT BY CONGRESSMAN WILLIAM CARNEY, RANKING MINORITY MEMBER, SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT

Thank you, Mr. Chairman. I would like to compliment you for holding this hearing, as the problem of drug lag is a serious and continuing one. Your leadership in raising this issue, and in addressing the difficulties of the medical community and the pharmaceutical industry in bringing vital new drugs to the marketplace represents the highest use of the congressional hearing process. Only by bringing these problems to the attention of the public and the Congress can we expect to identify solutions, and only by following through on these problems as you have done can we hope to see these solutions implemented. You are to be commended for your continuing leadership on this matter.

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Mr. Chairman, that is all I have to say, and I thank you for the opportunity to make this opening statement. As we begin the hearing, I would like to note the remarks made earlier this year by Health and Human Services Secretary Schweiker, who said, "I plan to break the inertia that has prevented clear and decisive improvement in the regulation of new drugs in the United States." I hope our witnesses will tell us that we are on the way towards achieving this goal.

Mr. SCHEUER. Before you introduce the next witnesses, let me thank you very much for your willingness to involve yourself in this issue. We welcome your leadership, and we welcome your insights from your past experience in the industry. And we thank you very much for coming here this morning.

Ms. FIEDLER. It's my pleasure. Thank you.

It is my privilege this moring to introduce Mr. Henry Gackstetter, his daughter Michele, and wife Carol, who have come here from southern California on a courageous mission. They will share with us the story of Michele's valiant fight against SSPE, a rare neurological disease, and her successful treatment by the use of Isoprinisine, a drug which has not yet been approved by the FDA for general use. I hope that the committee will give full and careful consideration to their important testimony.

Mr. SCHEUER. Well, it's a pleasure to welcome Henry Gackstetter and Miss Shelly Gackstetter. I've had the pleasure of meeting with them formally and informally before now.

Now, Michele, I want you to just think that we're sitting in the living room and chatting with us, and that there isn't any big hearing room and there isn't any big U.S. Capitol, that we're just sitting in the living room talking together; OK? So you just talk to us as if we're sitting on a couple of sofas.

Mr. Gackstetter, your testimony and that of Shelly will be printed in full in the record as you have it prepared. So perhaps you might just talk with us informally or read the testimony, whichever you prefer, however you feel most comfortable.

STATEMENT OF HENRY C. GACKSTETTER AND MICHELE GACKSTETTER, SUNLAND, CALIF.

Mr. GACKSTETTER. Thank you, Mr. Scheuer, Ms. Fielder, members of the subcommittee, Mr. Shacknai, for this opportunity to discuss with you our experiences with the drug Isoprinisine, the FDA and associated agencies in our ongoing effort to sustain the life of

my daughter, Michele, and to assist in any way possible to find a cure for SSPE, or subacute sclerosing panencephalitis.

You've already been introduced to my daughter, Michele, and her mother, Carol. We live at 10512 Sunland Avenue in Sunland, Calif. It's a San Fernando Valley suburb of Greater Los Angeles. And we're there because Shelly attends a special school for young adults called Tierra del Sol.

I'm a business consultant, and currently general manager of a company in San Fernando, Calif.

Michele, and all her friends call her Shelly, was born November 10, 1959, in Toledo, Ohio. She was a bright, aggressive, quick-responding, quick-learning and all-around ideal daughter. At the age of 5,. in approximately 1964, Shelly contracted a normal case of childhood measles, and probably as a result of exposure to them from her brothers and sister in the environment in which we lived in North Branford, Conn. There were no unusual symptoms to the case of the measles, nor any apparent visible side or after effects. Shelly, as well as her three brothers and sister, recovered and progressed normally.

As part of the preschool and elementary health program in the Connecticut school system, Shelly, along with her brothers and sister, received the measle vaccine in approximately 1965. As I said before, there were no unusual side or after effects from the measle vaccine.

Shelly was an outstanding student through the fourth grade of elementary school in Connecticut, receiving top grades and honors in all subjects, including music, where she was well along the way to mastering the flute. She was active in Brownies, and a very vital and vibrant part of the family.

Shelly was, and is, a part of a large family, the third of five children. She has two older brothers, Michael and Douglas, who are electronic engineers and nuclear engineers respectively, in the U.S. Navy, and a younger sister, Denise, who is studying art at the University of Wisconsin, in Madison, and a younger brother, Stephen, who graduated from high school in Sunland, Calif.

During an annual summer vacation at the family farm in Ohio in July of 1970, Michele experienced a minor accident in a fall from her bicycle. This caused a minor laceration of her thumb which was treated by a general practitioner, Dr. Ridenaur, in nearby Elmore, Ohio, who was our family physician when we lived there. Normal throbbing from the laceration occurred, and after 2 days it appeared that the throbbing was abnormal because it was not subsiding. Phenobarbital and mobilization of the arm was recommended by the general practitioner with no beneficial effect.

At that time we became suspicious that the problem was greater than a minor injury, and when we returned to our home in Connecticut, in North Branford, Conn., a suburb of New Haven. Our family doctor, Dr. Norman Levy, recommended us and Shelly's problem to an associate of his, Dr. Richard Mattson, who was working with the School of Medicine at the Yale University Medical Research Center.

Careful and extensive testing of Shelly's condition, including both blood tests and a spinal tap, identified Shelly's problem as subacute sclerosing panencephalitis. At that time, Dr. Mattson de-

scribed to us in very careful detail the very terrible and tragic consequences of this illness.

SSPE, as it has come to be known, is a measle antibody infection of the spinal fluid that attacks the base of the brain. The exact cause of the problem has not been defined, at least to us. Several theories exist. The facts of the illness are an onset of agitation, mioclonic seizures, which are jerking motions, of the arms and legs, speech interruption, the loss of the ability to read and to write, and the eventual loss of the ability to walk and maintain balance. Second stages of the disease are hallucinations, hysteria, lack of body function control.

The third stage is comatose, and the final stage is death.

Dr. Mattson advised us at the time of diagnosis that the normal progression of the disease was terminal within a period of 6 to 18 months.

At the time of diagnosis, Shelly was administered doses of both Dilantin and Valium as tranquilizers and to help control the mioclonic seizures. I would point out that in Shelly's case, the mioclonic seizures occurred every 20 seconds for approximately two-tenths of a second. During that seizure, any motion, speech, thought process, or sight was interrupted. If she was walking, she stumbled; if she was holding a glass, she dropped it; if she was speaking, she stuttered; if she was looking, she blinked, and if she was thinking, she lost the thought train.

One need not concentrate or consider too long the effects of total interruption of functions every 20 seconds to appreciate the level of confusion and the great road blocks established that nearly prevented any progress in learning.

Shelly rapidly went from the head of her class to a period of having great difficulty in maintaining anything approaching a normal learning curve.

Within a period of 4 months she began to experience hallucinations. By this time it had been necessary to take her out of the normal school environment, and she began to see and feel "insects" on her body, especially when she tried to sleep. She was very disturbed by the presence of even shadows.

All during this time she was under the treatment of Dr. Mattson.

By February 1971, slightly more than 6 months after the initial diagnosis of SSPE, it was apparent both to Dr. Mattson and to us that the deterioration of her condition was accelerating. After a long discussion with Dr. Mattson and with other neurologists from Harvard and several other respected medical institutions, it was decided Shelly's only hope was to try an experimental medication that had come to the attention of Dr. Mattson in his investigation of medical research journals. This medication was isoprinisine.

Dr. Mattson informed us at that time that very little was known about isoprinisine, remembering that this was very early in 1971. However, he told us that early experience with the drug had indicated positive reaction in different kinds of illnesses, including, I believe, Parkinson's disease. There was at that time no other known cure or hope for Shelly, and Dr. Mattson reviewed carefully with us the fact that isoprinisine was not necessarily a cure. However, there was a possibility that it could arrest the rapid progress of the deterioration she was experiencing. Given that chance, her

own body chemistry and willpower, and with the help of the Lord, she might work her way back to a reasonably normal existence.

It was agreed by all parties, including Shelly herself, that prior to the administration of the medication a brain biopsy be performed to determine the atrophy that may have occurred. Shelly was admitted to the Yale New Haven Hospital and the biopsy was performed early in February 1971. The results of the biopsy indicated that very little, if any, atrophy existed, and at that point we agreed that Shelly should be the first child on record to receive isoprinisine for the purpose of attempting to arrest the deterioration of SSPE.

Shelly began, shortly after the biopsy, to take 10 tablets of isoprinisine each day, 3 in the morning, 2 at lunch, 3 at dinner, and 2 before retiring. She returned home from the hospital to convalesce in the environment of her brothers and sister. Her older brothers were especially supportive. She was unable at that point to return to school. Because of the large family environment, she was never eliminated from family activity. She was constantly subjected to the learning experience and encouraged to continue to try within her ability to maintain some level of progress.

The family gathered together nightly for Bible readings before retiring, and Shelly once again was included. Her Bible was held open to the appropriate verses being read and, when her turn came, we read the passage for her carefully and slowly following each word with our fingers as she strained to try to identify. She never gave up.

After about 45 days we noted that the mioclonic seizures or jerking had begun to subside significantly. There were less problems in handling knives and forks in the simple process of eating or drinking. Her ability to recognize objects, like a McDonald's sign, began to improve. Then one night in the middle of one of the Bible sessions, suddenly and without any coaching, she was able to identify and read correctly a series of seven or eight words from the pages of her Bible. This was the first real sign that the connective systems in her brain were coming back into function.

By the fall of 1971, Shelly was able to return to school to special learning classes to begin to pick up where she had left off nearly a year earlier.

She continued to see Dr. Mattson on a monthly schedule, and continued to take the isoprinisine. Very, very slowly she began the road back. These weren't easy times, because her peers in school, as young people are prone to be, are not always compassionate and understanding for people with special problems. But with the help of her teachers and the encouragement of her brothers and sister, and her will power to continue, she was able to graduate from elementary school only a year behind her normal schedule.

With the move of the family from New England back into the Midwest, specifically to Fond du Lac, Wis., Shelly transferred from the care of Dr. Mattson to Dr. Peter Huttonlocher at the University of Chicago Medical Research Center. By 1979, almost 8 years after she began taking isoprinisine, Shelly's dosage level had increased to 15 tablets daily, and she graduated from Goodrich High School in Fond du Lac, Wis., with a full diploma. This was one of the highlights in Shelly's life.

During the time that we lived in Connecticut and were working with Dr. Mattson, and subsequently in our experiences with Dr. Huttonlocher, and because of Shelly's experience with isoprinisine, we came to know the parents and the children of families reeling under the tragedy of a loved one who had contracted this terrible malady.

It appears to strike the most vibrant, active members of any specific family. I have sat many times beside the bed in hospitals of young people, girls and boys, and have listened to their parents talk about the physical and mental agility of these young people prior to the onset of the disease, budding gymnasts, cheerleaders, people excelling academically or socially, and in sports, beautiful young people lying there consumed by seizure, confused, having difficulty communicating, looking out at the world for help and asking, "Why me?"

We only hope they had, and have today, this isoprinisine and its very apparent proven ability to arrest the deterioration of the disease and give the body the ability to prevent further decline.

Mr. Chairman, I am not a doctor nor a chemist, I am a father. I have seen my daughter, held her, and heard her go from the top of the world to the depth of what still is an incurable problem. I have seen and experienced with her the use of isoprinisine, and, gentlemen, counsel and friends, she sits here beside me today, more than 10 years after the doctors said she had 6 to 18 months to live.

[Ms. Gackstetter weeping.]

Mr. GACKSTETTER. Our apologies.

Mr. SCHEUER. There is no need for apology.

Mr. GACKSTETTER. Mr. Chairman, you can appreciate our concern, anger, and subsequent motivation to take serious issue in every possible way with the decisions and recommendations of Dr. Marian Finkel, Associate Director for New Drug Evaluation at the FDA, as reported in an article in the Wall Street Journal in 1980.

Isoprinisine is not readily available. Shelly receives it under an experimental license. Although we live in Sunland, Calif., today, and the drug is produced in Newport Beach, it is mailed to Chicago, to the University of Chicago Medical Research Center, and then back to us, because that's where the experimental permit was transferred. The paperwork required to move these experimental permits is incredible.

We were fortunate because we lived in Connecticut, nearby Yale New Haven Research Center, and our family doctor happened to know a research neurologist who was working in this area, and who was cognizant of the state of the art of development. And Shelly survives today because of that coincidence.

When we moved from New England to another part of the United States, we did it because that's where the other research area was located.

We have seen many children, many families, who, only after long searching, have finally come into contact with the drug. And it is important to note that it is critical for these young people to receive the Isoprinisine early in the onset of the problem before atrophy occurs. Because if it's too late, even though the drug arrests the progression, the ability to come back is seriously impaired.

I submit, ladies and gentlemen, that progress must be made. Our family supports careful testing and evaluation of potential side and after effects of any compound that is to be ingested or applied to a human being. It is incumbent on all of us to remember that we have to recognize that the basic goal is to cure illness and promote life, not to proliferate testing.

The problem, the challenge, in this case SSPE, is here, and there are volunteers who are willing to try a compound that has historically proven to have no adverse side or after effects and for which there exist many well documented cases of significant improvement. No power on Earth, and most certainly not the U.S. Government or its agencies, should in any way interfere with the organized, monitored application of this medication to the people who have the need and desire to use it.

Shelly's not cured, not yet. We talk about her problem on a daily basis, and we pray with her that the good Lord will help us and the many dedicated people somehow to find a cure in time for this devastating illness, and not in any way be delayed by an insensitive megalithic governmental agency.

Mr. Chairman, your subcommittee is part of this dedicated group. Your enthusiasm in developing guidelines for the agencies to expedite, judiciously, new medications approval will save thousands of lives and improve the quality of life in the future.

Thank you for this opportunity to be a part of the democratic process. If you have any questions, I will do my best to provide you with factual and objective-as-possible answers.

Mr. SCHEUER. Thank you very much, Mr. Gackstetter, and thank you, Shelly, for having been part of our congressional process, part of our deliberative process.

These hearings are organized for the purpose of informing Members of Congress on subjects on which we have to legislate. And, Shelly, you have played an integral part in our research and in our better informing ourselves, and in better preparing ourselves to meet the problems of people like you who are struggling so courageously with an illness that we still don't fully understand.

Shelly, I want to repeat what I told you yesterday and the day before: You have been an inspiration to me, and I'm sure you are an inspiration for everybody in this room.

I just have a couple of questions, and my colleagues, I'm sure, will have a question or two for you, Shelly.

I take it you feel, do you not, that Isoprinisine has saved your life?

Ms. GACKSTETTER. Yes.

Mr. SCHEUER. And has enabled you to start on the road to recovery?

Ms. GACKSTETTER. Yes.

Mr. SCHEUER. Do you feel that other people suffering from SSPE should also be allowed to have Isoprinisine available to them conveniently near their homes?

Ms. GACKSTETTER. Yes.

Mr. SCHEUER. And without the hassle that you and your dad and your mother have had to go through?

Ms. GACKSTETTER. Yes.

Mr. SCHEUER. Shelly, we're very proud of you, along with your parents, who must be just busting out with pride at your marvelous accomplishment in finishing high school.

What do you plan to do now?

Ms. GACKSTETTER. I plan on going to college.

Mr. SCHEUER. And what will be your special interest in college?

Ms. GACKSTETTER. I'm going to become a nurse.

Mr. SCHEUER. Well, Shelly, I just want to repeat that your conduct and your courage and your determination have been a great inspiration to me.

Congressman George Brown of California has a question or two.

Mr. BROWN. Mr. Gackstetter, do you have any information about the status of the drug as a result of the use by your daughter and others on a compassionate basis? Has there been accumulated enough clinical data now to proceed with the rest of the process of approving the drug?

Mr. GACKSTETTER. I'm not certain, Mr. Brown. I do know that we still receive it on an experimental basis. I'm not aware of any specific dates as far as overall approval is concerned. We continue to work in that area.

Mr. BROWN. Well, we can get that information from other sources. But it's one of the things that has troubled the committee, I think, that we have failed to take advantage of the information garnered either in other countries or in special instances within our own country, to expedite the approval process. I was wondering whether we could benefit from the experience you've obviously been in for the several years that Shelly has been on the drug, and from others, also. I'd like to know why we couldn't proceed with the approval on a formal basis. And I trust other witnesses will clarify that for us.

Mr. GACKSTETTER. Certainly Shelly has taken a great deal of the medication, Mr. Brown.

Mr. BROWN. I notice that she counted 33,000, or so; many pills.

Mr. GACKSTETTER. We were figuring it up the other night as we prepared the presentation for the hearing here, and it comes to more than 38,000 tablets of Isoprinisine over a period of 10 years.

Mr. BROWN. Well, that should provide a large body of experience for us.

I have no further questions.

Mr. SCHEUER. Well, I want to thank you, Mr. Gackstetter, and thank you again, Shelly, for helping us do our job better, helping us to sharpen our perceptions, sharpen our insights, and just make us more aware of the terribly important job that has to be done in making new drugs available to young people like you as soon as they are proved to be safe and effective, and without the heartbreaking delays that are occurring now due to the incredible bureaucratic processes that impede getting drugs to people who need them most. We are working on them, and with your help and support we will make progress.

We'll keep in touch with you, Shelly, as you move ahead in your career and become a nurse. I know that as the years go on we're going to take more and more pride in your great accomplishments.

We congratulate you on your courage and your guts, on your stick-to-it-iveness. Do you know what that means, stick-to-it-ive-

ness? It means that when you make up your mind to do something, by gosh, you do it. It's a wonderful, wonderful characteristic. You've made us all very proud to be part of the process in which you have helped us do a better job in meeting our responsibilities as Members of Congress.

I want to thank you, Congresswoman Fiedler, for your help this morning. It shows a very great sense of compassion, and we very much appreciate it.

Mr. GACKSTETTER. Thank you, Mr. Congressman.

Mr. SCHEUER. Thank you.

Now we'll hear from Shelly's doctor, Dr. Paul Dyken, chief of the department of pediatric neurology, University of Georgia Medical School.

We're very happy to have you here, Dr. Dyken. Your testimony will be printed in full in the record. It's fairly brief testimony. You can either read it or, if you prefer, we'd be happy to have you just chat with us informally.

STATEMENT OF DR. PAUL DYKEN, CHIEF, DEPARTMENT OF PEDIATRIC NEUROLOGY, UNIVERSITY OF GEORGIA MEDICAL SCHOOL

Dr. DYKEN. Thank you, Mr. Chairman, members of the committee.

My name is Paul Dyken. I'm professor and chief of the section of pediatric neurology, at the Medical College of Georgia, which is in Augusta, Ga. I have really nothing to add over my printed statement, and certainly, as a human, nothing to add to the very emotional testimony that preceded me.

I think that perhaps the best way that I can be of aid to your committee is to allow any questions which you might wish to ask me. Perhaps I can clarify some of your confusions in regard to the disease. Subacute sclerosis parencephalitis—which is a rare neurological disease which possibly represents complication of measles, that is, ordinary natural measles or rubela. Fortunately, a very rare complication of that disorder.

The name is quite long, and even we as medical scientists prefer to refer to it by its initials, SSPE, rather than by the whole name.

The disease itself was described many years ago. Still, we have had a rather long experience with it over the last 50 years here in the United States.

Besides being a professor at the Medical College of Georgia, I'm also the director of the National SSPE Registry, which has been in existence for about 10 years. We try to accumulate all the names and medical information on patients who are reported to have this tragic disease in the United States. Actually, in that sense, I'm not Shelly's physician, but I'm aware of her case because of my connection with this registry.

In the registry, we now have records on over 600 patients with this problem. This might give an estimate of the relative uncommonness of the disease.

SSPE is a rare disease that is usually considered to be untreatable. Other than possible experimental medicines in the past, there has been no specific medicine that we are using which was proven

to be helpful in stopping the relentlessly progressive cause of this disorder. Fortunately, perhaps, this is changing somewhat as time passes. There are also now improved therapies.

At one time the disease was considered absolutely incurable. The duration of the disease usually lasted from between 1 and 3 years. The process rarely went into spontaneous remission, although this did occur. About 90 percent of the cases were, at one time at least, thought to result in death within 3 years.

I've been fortunate enough to be able to use the drug Insosiplex or Isoprinisine on a relative handful of patients, (i.e. less than 20, over 15). Recently the results of our studies with Isoprinisine have been accepted for publication.

Of the 15 patients that we reported upon, we found that over half of them survived over 5 years. Of the 15 patients I have treated, only 4 have died; 11 are still living. One of these 11 went into a period of equilibrium, that is, there was a leveling off of the disease process, which, in itself, might be a success story, since the disease itself goes progressively downhill in 90 percent of the cases, as I mentioned before.

The other 10 patients all showed improvement, 8 of these directly related to the beginning of treatment with Isoprinisine. Two patients showed delayed beneficial response several months after Isoprinisine was first given.

Some of these improvements, I must be honest, have not been as dramatic as others. Some have still left the patient with a considerable disability. But, very encouraging, some responses have been dramatic. One of my patients is now married and is able to carry out running a simple household. Another went for almost 6 years with very minimum disability. This latter patient, on a 100-point scale, had 5 percent disability for many years.

Thus, there are occasional dramatic improvements with the drug. But in the majority of them there has been some improvement.

I realize that it's very, very difficult from a statistical viewpoint to study rare diseases, particularly diseases that show some atypical features such as spontaneously improving. And it's very difficult without some question to measure these responses or to prove a treatment effect.

But I think there's been enough investigation on this drug. Dr. Huttonlocher, one of Shelly's physicians, has also had relatively considerable experience in treating this disease, with this drug. And I think most of the investigators who have used Isoprinosine are in agreement that there have been some definite beneficial effects from it.

As a physician I always must to ask myself the final question as does any physician who is ordered to treat human beings. That is, Would I use the treatment on myself or my family? My answer, in regard to Isoprinosine is, if I had SSPE or a member of my family did, without question I would use it at the current time before new theories are developed.

With this, I would certainly be glad to try to answer any questions.

[The prepared statement of Dr. Dyken follows:]

TESTIMONY OF DR. PAUL DYKEN BEFORE THE SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH AND ENVIRONMENT ON SEPTEMBER 16, 1981

I am pleased to be here to relate any personal experiences in the care and treatment of children and young adults afflicted with subacute sclerosing panencephalitis, or SSPE as it is more commonly referred. Later in the presentation, I will clarify the relationship between these experiences and the "drug lag," which is the primary issue being addressed today at this hearing.

First of all, I think it is important to briefly define SSPE so we may all understand the nature of the disease process. SSPE is a rare, childhood neurological degenerative disease that is thought to be caused by a measles or measle-like virus infection. The initial manifestations of the disease are subtle and may include poor school performance, changes in behavior, speech impairment, involuntary movements and convulsions. In the second stage, the patient is overtly demented, stumbles a great deal, and develops characteristic, myoclonic jerks that are synchronous with certain patterns that can be seen on the EEG. Chorioretinitis is common. Most patients pass quickly into stage three. At this stage, the patient has lost all mental function and may become comatose with muscular rigidity. By stage four, the patient has lost all cortical functions and only medullary reflexes exist. He is subject to prolonged episodes of forced laughing or crying. Death usually results from vasomotor failure or supervening infections. In the classic form of SSPE, the disease is progressive and culminates in death from one to three years from onset.

Over the past 15 years or so since my completion of residency and postresidency training in neurology and pediatric neurology, I have seen approximately 30 cases of SSPE. Many of these patients were diagnosed prior to the availability of Isoprinosine, and their conditions, without exception, unrelentingly deteriorated until death. I should mention that this progressive deterioration to death occurred despite the utilization of a variety of experimental therapies that unfortunately proved to be ineffective. Since becoming Chief of the Division of Child Neurology at the Medical College of Georgia, I have treated eighteen patients with Isoprinosine®. Five of these patients have died, but thirteen are still alive. What is even more remarkable than the large percentage of survivors, is that many of these patients have shown clinical improvement while on the drug. The following data have been excerpted from a manuscript describing our clinical experience with the first fifteen Isoprinosine-treated SSPE patients that was recently submitted to a medical journal. Four of these patients followed a typical course for this disease and died (on the average) 9½ months after onset while eleven patients are still living from 25 to 147 months after onset. Of the eleven surviving patients, two stabilized and nine were clinically improved for variable periods of time. The duration of improvement for nine patients indicated that their beneficial responses were drug-related. Exacerbations occurred during treatment in three of the eleven survivors, but each had stabilized at the time the manuscript was written. None of the patients in the study displayed any symptoms of disease or toxicity which could not be ascribed to the natural course of SSPE even though some patients were on uninterrupted Isoprinosine treatment for almost 5 years. It should be emphasized that the results of our clinical study are consistent with an earlier published report entitled Isoprinosine in Subacute Sclerosing Panencephalitis (written by Drs. Huttenlocher and Mattson, who are pediatric neurologists, at respectively, the University of Chicago and Yale University), and is provided in my written testimony. I would like to add that as a medical scientist, it is always reassuring to know that colleagues in other institutes have recorded observations that are similar to your own.

At this time, I would like to comment on some recent events that I think are particularly relevant to a general discussion of what is termed the "drug lag."

In the last year and a half, I have participated in two meetings of the FDA's Peripheral and CNS Drugs Advisory Committee. The reason for my participation in these meetings can be directly attributed to my medical speciality, and rather extensive clinical experience with Isoprinosine in the treatment of SSPE. The first Advisory Committee meeting on June 13, 1980, was convened by the FDA to evaluate data collected by Newport Pharmaceuticals International, Inc. (the manufacturer of Isoprinosine) on the clinical course of SSPE in patients receiving the drug. Dr. Ira Lott from Harvard Medical School was among the participants and described his experience with Isoprinosine in SSPE. Since 1972, none of his seven treated patients had died which is impressive considering the inevitable mortality seen in untreated or historical SSPE controls. The recommendation from this first Advisory Committee was that Newport Pharmaceuticals should submit a New Drug Application to the FDA, and the Agency should then take positive action on this submission.

On March 30, 1981, a second meeting of the same Advisory Committee was assembled to discuss the data contained in Newport's NDA. The primary focus of this meeting was on the statistical analysis of the data as presented in the NDA. In this regard, the principal discussants representing Newport included Dr. Edmund Gehan, Professor of Biometrics at M.D. Anderson Hospital and Tumor Institute in Houston; Dr. Frank Stitt, President of Clinical Data Research Services in San Francisco; and Dr. Milton Alter, Chairman of the Department of Neurology at Temple University Hospital in Philadelphia. After considering all information available, including the scientific data as presented by Newport and its statistical consultants and the clinical experiences of several principal investigators of the drug in SSPE, the committee concluded that Isoprinosine was safe and effective in the prolongation of survival in this disease and the NDA should be approved.

It is my understanding, however, that despite the positive recommendations on safety and efficacy resulting from two impartial FDA Advisory Committee meetings, the FDA has indicated to Newport that their NDA is not approvable at this time. It appears therefore that the FDA is saying that their judgment transcends both that of their own Advisory Committee and the Company's consulting statisticians and independent medical scientists, many of whom are nationally and internationally renown. This intransigence on the part of the FDA would seem to be the predominant cause of the "drug lag."

In conclusion, I am convinced that Isoprinosine is safe and effective in the treatment of SSPE. Children afflicted with this disease, but receiving Isoprinosine therapy, have a higher probability of not only surviving but living an improved quality of life in comparison to untreated patients. I am hopeful that this committee will implement those policies that will insure Isoprinosine and other beneficial therapeutic agents can be prescribed by clinicians who are faced with treating a variety of diseases for which effective drugs are in existence but unavailable in the pharmacies of this country because the FDA is unwilling or unable to act in a responsive and responsible manner.

Mr. SCHEUER. Thank you very much, Dr. Dyken.

What would Shelly's prognosis have been without the Isoprinisine treatment? In other words, is there any alternative, are there any other options?

Dr. DYKEN. There is now no curative treatment for SSPE. There are palliative treatments. As you know, there are two forms of medical treatment: curative and palliative ones. If a person has a headache from a brain tumor, aspirin is a palliative treatment. The brain tumor might best be treated, however, by removing it. That's a curative treatment.

There is no curative treatment for SSPE at least that has stood the test of time. And there have been many attempts, obviously, to try to develop curative treatments. There have been few, with the exception of Isoprinisine. I believe that the action of Isoprinisine is one of a curative rather than a palliative nature.

All of our patients, of course, are also on anticonvulsant medications, antibiotics, those sort of things that one would consider to be palliative treatments.

Mr. SCHEUER. Do you feel that Isoprinisine should be made quickly and immediately available?

Dr. DYKEN. Yes, I believe Isoprinisine should be available.

Mr. SCHEUER. On a nonexperimental basis? It should be approved on a compassionate basis, perhaps, for all SSPE patients?

Dr. DYKEN. Yes, I do.

Mr. SCHEUER. Do you believe that pharmaceutical innovation of small firms like Newport are stifled by unnecessary regulation?

Dr. DYKEN. This is not my area of expertise, and I hope you take it in the proper context, but I believe that that's true.

Mr. SCHEUER. You refer to FDA intransigence in your testimony. What is the cause of that? What has your experience been?

Dr. DYKEN. I'm not sure that I can answer that accurately except to say the problems of bureaucracy, are important I believe.

Mr. SCHEUER. Do you have the feeling from your colleagues that there is frustration in the medical community with the drug approval process as it presently functions?

Dr. DYKEN. Yes; particularly in regard to treatment for rare diseases. I believe it's a bad situation.

Mr. SCHEUER. What do you think ought to be done about it?

Dr. DYKEN. I think they should loosen some of their controls.

I think that Mr. Gackstetter's statement was very good, and I think particularly the conclusions were very good.

There comes a time when the test becomes more important than the treatment. And I think at this stage, over the many, many years of experience with this drug, that it should be approved. It is a drug that's non-toxic, it hasn't produced any bad effects. Whether Isoprinisine is the final answer to the treatment of SSPE or not is another question; but I do strongly believe that Isoprinisine should be approved.

Mr. SCHEUER. Thank you.

Congressman Brown.

Mr. BROWN. Dr. Dyken, do you know specifically which stage of the approval process that the drug is in at this point?

Dr. DYKEN. No, I don't. I don't know any specifics about where it stands right now.

Mr. BROWN. The approval process—and I'm not at all expert in this either; but it is a rather long and complex process. The part that bothers me is whether the process is proceeding according to some normal expectations of speed in this case, or whether it is being delayed for one reason or another. Perhaps we can find this out from the FDA.

As I understand it, this drug is approved in other countries; is that right?

Dr. DYKEN. That's my understanding, yes. I think the last that I heard, that 51 countries have approved this drug, including England, France, and Italy.

Mr. BROWN. Do you know anything about the clinical results, the history of the experience with the drug in other countries? I presume the literature reflects that.

Dr. DYKEN. Yes, it does. In reviewing this a bit, I'm sure there are some countries that I've missed, but there has been a large study from Lebanon and other countries.

Mr. BROWN. Does the number of patients in these other countries compare with the 600 number you mentioned you have in the registry here?

Dr. DYKEN. Well, for some reason registries are quite frequent for SSPE. I don't know why that is. Mainly because it's a disease that combines epidemiological research—it's a good disease for those sorts of studies, and to have a registry of various patients is very popular.

I think there are now seven or eight national registries: one in Israel, one in Lebanon, one in Germany, one in England. The largest number of SSPE patients are in the United States. But, relatively speaking, this disease is relatively more common in the Near East, in Lebanon and in Israel, where they have maybe 100 or 150

patients in their registry, with a much smaller population than the United States, obviously.

Mr. BROWN. As another initiative of this committee we've been looking at the problems of medical information systems, of which the registry is a specialized item. I wonder if you could comment briefly on the registry in the sense of what contribution it makes to understanding research on the disease, and is it reasonably successful in terms of incorporating all of the cases and making the histories available to all researchers or others who might have need for the information. Is it organized in such a fashion to do that?

Dr. DYKEN. The U.S. Registry was initially started not quite 10 years ago by Dr. J. T. Jabbour at the University of Tennessee in Memphis.

Mr. BROWN. Can you explain to me how doctors do such a registration, something where he says "Well, I think a registry would be nice. Let's start one up."

Or does it require some more elaborate processing?

Dr. DYKEN. Probably a little bit more elaborate if you want to start it up, but that's how I think Dr. Jabbour first started it up. He said he wanted to collect the patients and at that time we had a medical organization called the Child Neurology Society. It was the first organized society of medical child neurologists, that is neurologists specializing in pediatric problems in the world, and this was founded about 10 years ago.

Dr. Jabbour was one of the initial early members of the clinical neurology society, as well as myself. He had an interest in SSPE because he had seen many patients with the disorder. Tennessee was the location of where the disease was first described in 1934. It remains to this day a core area for the disease. Having interest, Jabbour felt that a registry would be a good thing to publicize to the pediatric neurologists in the United States, in order to learn more about the disease's characteristics. There are now over 600 patients who have been reported to the registry with SSPE.

He wrote letters and asked chief neurologists and pediatricians to report cases to him. He wanted to develop this information, and that's basically how it started.

This registry has been supported by the Bureau of Biological Research which is part of the FDA. It's even now supported by operating funds from this bureau.

One year ago Dr. Jabbour decided that 10 years of this duty was enough. He then asked me if I would take over the registry. He suggested I transfer it to the State of Georgia which is also a large core area for SSPE. In fact possibly more cases are from Georgia now. The incidence of SSPE is much greater in the Southeastern United States than other areas of the country.

And so a year ago I took the registry over. At that time there were less than 600 patients. Since that time we have entered about 40 to 50 more. At last count I believe we have records on about 625 patients.

How is this data used? It's used by anyone who can assure me they are professional and will do all in their power to protect individual rights of confidentiality. We have had our greatest problem in the last year in doing the secretarial work necessary to transfer the data, that is, the file, computer tapes and that sort of thing. It

has taken a while to get it organized again. Most of our activities in the last year has been involved in trying to organize the data. Hopefully, soon this will be available to anyone interested in this particular disease. I plan to maintain an open policy—within limits, of course. All the data accumulated in our computers and files will be available to those who are appropriate in their demands and wish to use our data.

Mr. BROWN. You answered some of my questions. It is a computerized file and it is accessible, I presume, by phone to others who seek information from it. And I presume you have recorded data in a standardized format so that it can be interpreted.

Dr. DYKEN. We have files on every patient and we have information on every patient in our computer. By telephone? It depends on what kind of information one seeks. Obviously we have to protect the confidentiality of individuals.

Mr. BROWN. Now since the FDA supports this I presume that the FDA knows that it's there and uses data for purposes of validating treatment processes, the use of the drug, for example, and so forth. Is it used for that purpose?

Dr. DYKEN. Since it has only been in existence for 1 year in Augusta, no one has yet used it in this fashion other than myself. But Dr. Hautpman, a statistician from the FDA who I talked to recently when I was in San Francisco—yesterday—has made plans to come down to Augusta to extract information that might be useful in analysis of the data on Isoprinisine. He wishes to carefully look at the data on untreated control group.

Mr. BROWN. Well, that's the sort of thing I had in mind as to whether it was being used for that purpose.

Dr. DYKEN. It hasn't been to this point.

Mr. BROWN. It has not been used to——

Dr. DYKEN. It has not been used to this point.

Mr. BROWN. And yet this contains the largest or possibly the only systematic collection of data on the disease and the treatment.

Dr. DYKEN. I think it contains the largest but not the only, and perhaps not the best, because our files are still in a process of flux right now for the reasons I have said.

I think the Israeli Registry is perhaps a little bit more up-to-date at this point.

Mr. BROWN. Do you know whether some registries exist for the rare diseases that could be made use of in comparable ways to what is being suggested here?

Dr. DYKEN. Yes, there are several registries. I can't think of a specific one right now.

Mr. BROWN. But you know they're there.

Dr. DYKEN. I just thought of one. Reyes disease is an example.

Mr. BROWN. I presume, and I hope I'm not belaboring the point unnecessarily, but I presume that there is some systematic way in which these registries are coordinated and information about them is available to, say, the National Medical Library or something of that sort, so that there is at least to some degree an integration of the system. Or can you speak to that point?

Dr. DYKEN. Yes, I can. As an example, if someone wanted to get information on SSPE, they would probably know that there is a registry and where it is located. There is usually enough publicity

on our registry that they would know to contact the Medical College of Georgia, and me specifically. This is one of our objectives, to publicize to physicians that we are in existence. We write newsletters to various specialists, write articles on the disease, perform experiments and give scientific presentations.

But the information would not be cross-referenced in any particular other way. Physicians or the scientist would call me and make arrangements with me to use our data.

Mr. BROWN. Let me reiterate the point you made earlier. As far as you know, there are no known adverse side effects or after effects of Isoprinisine?

Dr. DYKEN. There has been none in my experience and I am aware of none by reviewing the literature.

Mr. BROWN. The only question is one of effectiveness?

Dr. DYKEN. That is the question. That's the only question as far as I'm concerned.

Mr. BROWN. I have no further questions.

Mr. SCHEUER. Just a last question or two:

I take it you feel the Israeli Registry is perhaps the best in the world.

Dr. DYKEN. I think it's the most complete because here there has been a break in the continuity of reporting.

Mr. SCHEUER. Does that include experience in cases all over the world or just in Israel?

Dr. DYKEN. Just Israel.

Mr. SCHEUER. Wouldn't it make sense for an orphan disease which is small as SSPE to have at least one registry someplace that kind of includes all the known cases in the world?

Dr. DYKEN. An international registry?

Mr. SCHEUER. Yes. There probably aren't more than a few thousand cases of this kind all over the world, are there?

Dr. DYKEN. I think not.

Mr. SCHEUER. Certainly not 10,000, apparently a small number of patients. Wouldn't it make sense to have the patients' medical histories in one place where they can be followed and analyzed and judgments made as to the effectiveness of this drug so that the FDA, for example, would have not a few hundred cases but at least a few thousand cases on which to make their judgments?

And the same thing with the World Health Organization and the regulatory agencies.

Dr. DYKEN. It's a very difficult thing to do, as you would know, with different languages and that sort of thing. I would think it would be difficult, if not impossible.

I think in a sense, at present we have an informal international registry. The various national registries get together at times. There are international symposia. In fact there will be one in Beirut, I think, next spring.

Mr. SCHEUER. If you, for example, developed a new, improved way of using Isoprinisine or Isoprinisine with something else, an important new technique that you had discovered that clearly seemed to help, would there be some way you could get that word out internationally?

Dr. DYKEN. Probably the best way to communicate in medical ways is to publish. In other words to write an article and publish it in medical journals. That, of course, is the way we've gone.

Dr. Huttenlocher published on Isoprinosine about 5 years ago. I hope to publish the studies I referred to. One article will come out soon. I think these are the ways that such information is communicated to other physicians.

Mr. SCHEUER. It seems to me when you're talking about cancer, heart, stroke, there you're talking about millions of patients, and probably publishing is the most efficacious way of getting the word out. But where you're talking about a disease that has only a few thousand patients, there ought to be some way of getting directly in contact with the patient or with their doctor, and assuming that the English language is the lingua franca of the medical community.

At any rate we thank you very much for your very helpful testimony. Dr. Dyken, you're performing a heroic job, a very compassionate job. You've invested a great deal of your life and your profession in it, and we thank you and congratulate you. Thank you very much.

Dr. DYKEN. Thank you.

Mr. SCHEUER. We will now hear from Mr. Edward Densmore, Deputy Director of the Division of Human Resources, General Accounting Office.

Mr. Densmore, I see you're well accompanied. Will all of you take seats at the table?

Mr. Densmore, will you introduce your colleagues for the record?

STATEMENT OF EDWARD A. DENSMORE, DEPUTY DIRECTOR, DIVISION OF HUMAN RESOURCES, GENERAL ACCOUNTING OFFICE, ACCOMPANIED BY SETH PATTERS, EVALUATOR, HUMAN RESOURCES DIVISION; DR. MURRAY GRANT, CHIEF MEDICAL ADVISER, GAO; RONALD A. VIEREGGE, SUPERVISORY EVALUATOR, DETROIT REGIONAL OFFICE; AND PHILLIP E. GODWIN, EVALUATOR, DETROIT REGIONAL OFFICE

Mr. DENSMORE. Yes, sir, Mr. Chairman.

On my left is Dr. Murray Grant, who is in the Human Resources Division and the Chief Medical Advisor of the General Accounting Office;

Mr. Seth Patters, who is in the Human Resources Division at the Food and Drug Administration;

And on my right, Mr. Ron Vieregge and Mr. Phil Godwin from our Detroit Regional Office, who are primarily responsible for the work that we're going to be discussing today.

Mr. SCHEUER. Very good.

We have a copy of your testimony and of course we read it with great interest. It's only three pages long as I recall. You are more than welcome to either read it or perhaps to chat with us informally. It will be reproduced in full in the record, so perhaps you'd like to simply chat with us and describe what you're doing and what your recommendations are to the FDA.

Proceed as you wish.

Mr. DENSMORE. What I'd prefer to do, Mr. Chairman, if I may, is summarize this statement.

We are pleased to be here today to discuss our review of the Food and Drug Administration's efforts to speed up its drug review process. Our prior report of May 28, 1980, to the Subcommittee on Science, Research and Technology indicated that FDA's drug review process was lengthy and that it took almost as long to approve important drugs as drugs of less importance.

Our report identified the following factors which we believe affected FDA's efforts to approve drugs in a timely manner:

FDA guidelines regarding documentation to be submitted with a new drug application and the formatting of such documentation were imprecise and subject to varying interpretations.

Scientific and professional disagreements between FDA and industry were not being promptly resolved.

FDA feedback to industry was slow or inadequate in notifying firms of deficiencies in NDA's.

FDA's chemistry and manufacturing control reviews were lengthy.

Pharmaceutical firms were submitting incomplete NDA's and were slow in resolving deficiencies noted by FDA.

Commenting on that report, FDA said that it would take certain actions that it believed would reduce the time required to process NDA's by 25 percent for important drugs and 15 percent for all others over a 3-year period.

Our objectives on this review were to analyze recent NDA approval data, actions taken by FDA as a result of our prior report, and other suggestions that had been made to speed up FDA's processing time to determine the extent of its progress.

On August 27, 1981, we sent a copy of our draft report on this review to the Secretary of Health and Human Services for comment. A copy of that draft was provided to you on August 28, pursuant to your request. The draft has not been fully reviewed within GAO and we have not yet received the agency's comments. Therefore, I would like to caution that the draft, including the recommendations, are subject to revision.

We compared FDA's processing times for all NDA's originally received in fiscal year 1976 and 1977 which were approved as of March 1978 with those received in fiscal years 1979 and 1980 which were approved as of March 1981. NDA's for important drugs received in fiscal years 1979 and 1980 were processed by FDA in an average time of 8.2 months, or 6 months faster than similar NDA's received in fiscal years 1976 and 1977.

In total, approval time decreased 6.6 months. In addition to reductions in FDA's review time, industry reduced the time it took to supply FDA with more data or to answer FDA questions regarding information in the NDA by 0.6 months. FDA approved 12 important NDA's in the pre-1978 period and 14 important NDA's in the post-1978 period.

During the same period, FDA was able to reduce its processing time for other drugs by 1.1 month while increasing the number of NDA's approved. In total, approval time decreased 0.7 months.

Although FDA decreased its review time of these drugs by 1.1 months during this period, industry increased the amount of time

it took to supply FDA with additional data or answer FDA's questions about the NDA by 0.4 months.

In fiscal years 1976 and 1977, FDA approved 48 NDA's in this category. In fiscal years 1979 and 1980 this number increased by 77 to 85 percent.

I would like to caution, Mr. Chairman, that FDA's progress as shown by this analysis is encouraging, but should not be used as an absolute measure of the reductions in processing time that may ultimately occur. As the table indicates, many NDA's included in our analysis had not been approved as of March 1981. Additional time and analyses of these NDA's are required to more accurately measure FDA's progress.

Although FDA has improved its processing time, problems still remain. For example, only two of FDA's six reviewing divisions reduced their review time. The other four divisions showed an increase in NDA review time. One of the four, however, significantly increased the number of NDA's reviewed.

Mr. SCHEUER. Isn't it also true that among the four where the approval time was lengthened were the most important drugs for heart and cancer? Is that not true?

Mr. DENSMORE. Yes, sir.

Mr. SCHEUER. So that in the real targets of opportunity, the FDA's performance deteriorated in those years.

Mr. DENSMORE. It took longer to approve the important drugs.

Mr. SCHEUER. Thank you.

Mr. DENSMORE. Although information on NDA processing time is computerized, it cannot be used to analyze FDA's progress in approving drugs because it is unreliable. In answering our requests for computerized information on NDA's submitted in 4 fiscal years, FDA manually verified all of the computer information and found numerous errors. As a result, all of our computations and analyses had to be manually derived and verified.

This was not the first time that the FDA had found errors in its computer data and had to verify the data and manually compute the analysis. An FDA official told us that he routinely does this for reports involving NDA approval times that are prepared for the Secretary of Health and Human Services and the FDA Commissioner.

Although FDA's efforts to expedite the drug review process have achieved some success, FDA has not eliminated all the obstacles which prevent more timely review and approval of NDA's. We reviewed 6 of 21 initiatives undertaken by FDA to achieve the goal it established in October 1978 to reduce drug review time. The six initiatives represent those that we and FDA considered to be among the most important. They involve:

FDA's efforts to improve its communication with industry by conducting conferences at the end of phase II clinical testing.

FDA's invitation to sponsors of important drugs to submit manufacturing and controls information early before their NDA is fully prepared and submitted to FDA.

FDA's priority review system to expedite processing of important new drug applications.

FDA's efforts to speed up its process for validating a sponsor's methods to test a drug's identity, quality, strength, and purity.

FDA's efforts to improve the timeliness of the work of the Division of Biopharmaceutics, which reviews studies of the drug's behavior in the blood.

And FDA's efforts to expedite reviews by the Division of Biometrics, which reviews statistical data in the NDA.

As of April 10, 1981, FDA had conducted end-of-phase-II conferences with about 24 drug firms and had invited another 18 to participate in such conferences when they completed phase II clinical testing.

To determine how drug firms viewed the effectiveness of the conferences, we contacted 30 firms that either participated or agreed to participate in end-of-phase II conferences. Those who participated characterized the conferences as excellent and helpful in identifying FDA's concerns.

As of July 12, 1981, FDA had identified 37 firms eligible to submit manufacturing and controls data before submitting their fully completed NDA's. As of that date, 10 firms had submitted NDAs but had not presubmitted manufacturing and contols data. Only five firms had submitted such data before submitting an NDA.

FDA's chemists advised us that presubmission can expedite the drug's review if the information submitted is complete and represents the firm's final decision on manufacturing and controls. If, however, the information is incomplete or is changed by the sponsor when the full NDA is submitted, FDA's chemists may have to duplicate much of their review.

Priority review is intended to give important drugs special attention so that their applications are handled as rapidly as possible. FDA has not, however, defined this policy or the means for reviewers to implement it in writing. Many reviewers advised us that they have not understood how the priority review policy is to be implemented.

Therefore, while some reviewers give important drugs high priority and make every effort to expedite their review, others do not and treat all NDA's on a first-come, first-served basis.

We interviewed 41 chemists and medical officers who were responsible for reviewing important NDA's originally received in fiscal years 1979 and 1980. Fourteen told us they were unaware that important drugs were to be reviewed before others and that they reviewed drugs in the order received, regardless of therapeutic classification. Twenty-seven said that they knew of the policy and that they review important drugs before other drugs.

Despite FDA's initiatives to speed up validation of analytical methods proposed by drug firms, validations are often delayed and are sometimes the sole factor delaying NDA approval. Methods validation involves an FDA laboratory verifying proposed test methods for insuring the quality, strength, purity, and identity of a drug. FDA has established a 45-day goal for performing this function.

As of July 14, 1981, FDA had completed methods validations on 14 of 41 important drugs submitted for review during fiscal years 1979 and 1980. Our analysis showed that methods validations averaged 182 days for the 14 important NDA's. None of the 14 were validated within 45 days. One method was validated in 47 days and

another in 62 days. Time required to validate methods in the remaining 12 NDA's ranged from 104 to 411 days.

Efforts to speed up the reviews of the Division of Biopharmaceutics, which reviews such things as the rate of dissolution of a drug in the blood, have not been totally successful.

FDA officials told us that biopharmaceutical reviews are delayed because biopharmaceutical studies are not consolidated into a single section of the NDA, data requirements are not adequately communicated to NDA sponsors, and many requests for biopharmaceutical reviews are not made until late in the NDA review.

FDA also recognized that poor coordination existed between biopharmaceutics reviewers and other FDA reviewers of NDA material.

Another factor which has delayed biopharmaceutical reviews is the untimely request for these reviews by the Office of New Drug Evaluation. For all important drugs received in fiscal years 1979 and 1980 that had biopharmaceutical reviews, requests for these reviews were received an average of 133 days after receipt of the NDA.

Efforts to speed up the reviews of the Division of Biometrics, which examines the statistical data in the NDA, have also not been totally successful. FDA recognizes that statistical reviews have contributed to delays in FDA reviews and that improved coordination was needed between reviews conducted by medical officers and statisticians.

To improve the coordination FDA included representatives of the Biometrics Division in monthly staff meetings to discuss problems they encountered and the priorities for reviewing various NDA's. Nevertheless, FDA officials told us that statistical reviews continue to be delayed.

As early as March 1978, the Commissioner of FDA expressed the agency's intention to rewrite its regulations on IND's and NDA's. The Director, Bureau of Drugs, in a statement in December 1980, said that the proposed revisions of the IND/NDA regulations are undoubtedly the most important activity in the IND/NDA area during the 1980's, yet as of August 1981, a draft of the regulations had not been released for public comment.

The FDA has advised us that a draft of the revised NDA regulations should be published by March 1982 and that these regulations will probably not become final for at least 2 more years.

A draft of the revised IND regulations is not expected to be published for comments until October 1982.

In addition to the initiatives discussed, FDA is considering changing the requirements and handling of post-1962 generic drugs. The change would reduce the extensive industry testing and FDA review of drugs whose equivalents have already undergone effectiveness and safety approval by FDA and consolidate the review of generic drugs under one division.

If this is accomplished, FDA believes that additional industry and scientific personnel will be made available to review and approve at a faster rate drugs offering new therapeutic advances. This change is also intended to speed up the review of generic drugs which are generally made available to the consumer at less cost than the innovative drugs.

We believe that while the change may speed the review of important drugs, the review of generic drugs may be delayed because generics now processed by FDA's Office of New Drug Evaluation will be transferred to another Bureau of Drugs division which has a large backlog of unapproved applications.

If additional reviewers can be found within the agency to assist with the increased workload, delays in reviewing generic drugs may not occur.

We believe that implementing this proposed policy change requires close scrutiny by the Office of the Commissioner to assure that unexpected adverse impacts are minimized.

Mr. Chairman, this concludes our statement. We will be pleased to answer any questions that you or other members of the subcommittee may have.

[The prepared statement of Mr. Densmore follows:]

UNITED STATES GENERAL ACCOUNTING OFFICE
WASHINGTON, D.C. 20548

FOR RELEASE ON DELIVERY
Expected at 10:00 A.M. EDT
September 16, 1981

STATEMENT OF
EDWARD A. DENSMORE, DEPUTY DIRECTOR, HUMAN RESOURCES DIVISION
BEFORE THE
SUBCOMMITTEE ON NATURAL RESOURCES, AGRICULTURE RESEARCH
AND ENVIRONMENT, HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY

ON THE
FOOD AND DRUG ADMINISTRATION'S
EFFORTS TO SPEED UP THE DRUG REVIEW PROCESS

Mr. Chairman, and members of the Subcommittee, we are pleased to be here today to summarize and discuss our review of the Food and Drug Administration's (FDA's) efforts to speed up its drug review process. Our prior report of May 28, 1980, to the Subcommittee on Science, Research and Technology indicated that FDA's drug review process was lengthy and that it took almost as long to approve important drugs as drugs of less importance. Our report identified the following factors which we believed affected FDA's efforts to approve drugs in a timely manner:

--FDA guidelines regarding documentation to be submitted with a new drug application (NDA) and the formatting of such documentation were imprecise and subject to varying interpretations.

--Scientific and professional disagreements between FDA and industry were not being promptly resolved.

--FDA feedback to industry was slow or inadequate in notifying firms of deficiencies in NDAs.

--FDA's chemistry and manufacturing control reviews were lengthy.

--Pharmaceutical firms were submitting incomplete NDAs and were slow in resolving deficiencies noted by FDA.

Commenting on that report, FDA said it would take certain actions that it believed would reduce the time required to process NDAs by 25 percent for important drugs and 15 percent for all others over a 3-year period. Our objectives on this review, which was made at your request, were to analyze recent NDA approval data, actions taken by FDA as a result of our prior report, and other suggestions that had been made to speed up FDA's processing time to determine the extent of its progress.

On August 27, 1981, we sent a copy of our draft report on this review to the Secretary of Health and Human Services (HHS) for comment. A copy of that draft was provided to you on August 28 pursuant to your request. The draft has not been fully reviewed within GAO and we have not yet received the agency's comments. Therefore, I would like to caution that the draft, including the recommendations which are discussed in my statement, are subject to revision.

EFFORTS TO SPEED UP THE DRUG REVIEW PROCESS ARE ENCOURAGING--BUT PROGRESS HAS NOT BEEN CONSISTENT THROUGHOUT THE AGENCY

We compared FDA's processing times for all NDAs originally received in fiscal years 1976 and 1977 which were approved as of March 1978 with those received in fiscal years 1979 and 1980 which were approved as of March 1981. As shown in the following table, NDAs for important drugs received in fiscal years 1979 and 1980 were processed by FDA in an average time of 8.2 months, or 6.0 months (42 percent) faster than similar NDAs received in fiscal years 1976 and 1977 which had been approved as of March 1978. In total, approval time decreased 6.6 months. In addition to reductions in FDA's review time, industry reduced the time it took to supply FDA with more data or to answer FDA questions regarding information in the NDA by 0.6 months. FDA approved 12 important NDAs in the pre-1978 period and 14 important NDAs in the post-1978 period.

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Comparison of NDA's Received and Approved
in Fiscal Years 1976-77 and 1979-80

Category	NDAs a/ received	NDAs approved	Approval rate (percent)	Average time to approve: Total time	FDA time (months)	Industry time
Important drugs:						
1976 & 1977	35	12 b/	34	15.5 b/	14.2	1.3
1979 & 1980	41	14 c/	34	8.9 c/	8.2	.7
Increase (Decrease)			-0-	(6.6)	(6.0)	(.6)
Other drugs:						
1976 & 1977	197	48 b/	24	12.1 b/	11.1	1.0
1979 & 1980	239	85 c/	36	11.4 c/	10.0	1.4
Increase (Decrease)			12	(.7)	(1.1)	.4

a/The number of NDAs received was adjusted to exclude NDAs which were not appropriate to the analysis, such as NDAs that FDA refused to file because they were incomplete, later transferred to another Bureau, or canceled or that could not be approved because of pending litigation.

b/As of March 31, 1978.

c/As of March 31, 1981.

During the same period, FDA was able to reduce its processing time for other drugs by 1.1 months (10 percent) while increasing the number of NDAs approved. In total, approval time decreased 0.7 months. Although FDA decreased its review time of these drugs by 1.1 months during this period, industry increased the amount of time it took to supply FDA with additional data or answer FDA's questions about the NDA by 0.4 months. In fiscal years 1976 and 1977 FDA approved 48 NDAs in this category. In fiscal years 1979 and 1980 this number increased by 77 percent to 85.

We would like to caution, Mr. Chairman, that FDA's progress as shown by this analysis is encouraging, but should not be used as an absolute measure of the reductions in processing time that may ultimately occur. As the table indicates many NDAs included in our analysis had not been approved as of March 1981. Additional time and analyses of these NDAs are required to more accurately measure FDA's progress.

Although FDA has improved its processing time, problems still remain. For example, only two of FDA's six reviewing divisions reduced their review time. The other four divisions showed an increase in NDA review time. (See appendix.) One of the four, however, significantly increased the number of NDAs approved.

Because some reviewing divisions have increased their review time, we believe additional management scrutiny of these divisions may provide opportunities to further reduce processing times. Also, FDA needs to improve the reliability of its computer data in order to provide an accurate basis for monitoring its progress.

MEASUREMENT OF PROGRESS IS HAMPERED BY UNRELIABLE COMPUTER DATA

Although information on NDA processing time is computerized, it cannot be used to analyze FDA's progress in approving drugs because it is unreliable. In answering our request for computerized information on NDAs submitted in 4 fiscal years, FDA manually verified all of the computer information and found numerous errors.

As a result, all of our computations and analyses had to be manually derived and verified.

This was not the first time that FDA had found errors in its computer data and had to verify the data and manually compute the analysis. An FDA official told us that he routinely does this for reports involving NDA approval times that are prepared for the Secretary of Health and Human Services (HHS) and the FDA Commissioner.

RECOMMENDATIONS TO THE SECRETARY OF HHS

We are recommending that the Secretary direct the FDA Commissioner to

--develop a system to measure FDA's progress in meeting its goals of reducing new drug approval time,

--develop an accurate computerized data base on which such a system would draw and correct the errors in the existing computerized data base, and

--publish annually quantitative data showing approval rates for each type of drug (new molecular entities, new salts, new formulations, etc.) by each reviewing division.

FDA'S INITIATIVES TO EXPEDITE DRUG REVIEW HAVE BEEN ONLY PARTIALLY SUCCESSFUL

Although FDA's efforts to expedite the drug review process have achieved some success, FDA has not eliminated all the obstacles which prevent more timely review and approval of NDAs. We reviewed 6 of 21 initiatives undertaken by FDA to achieve

the goal it established in October 1978 to reduce drug review time. The six initiatives represent those that we and FDA consider to be among the most important. They involve:

--FDA's efforts to improve its communication with industry by conducting conferences at the end of phase II clinical testing.

--FDA's invitation to sponsors of important drugs to submit manufacturing and controls information early before their NDA is fully prepared and submitted to FDA.

--FDA's priority review system to expedite processing of important new drug applications.

--FDA's efforts to speed up its process for validating a sponsor's methods to test a drug's identity, quality, strength, and purity.

--FDA's efforts to improve the timeliness of the work of the Division of Biopharmaceutics, which reviews studies of the drug's behavior in the blood.

--FDA's efforts to expedite reviews by the Division of Biometrics, which reviews statistical data in the NDA.

END-OF-PHASE-II CONFERENCES HAVE IMPROVED COMMUNICATIONS WITH INDUSTRY

Clinical testing of new drugs is conducted in three phases: phase I, clinical pharmacology, involves the initial introduction of a drug in humans; phase II, clinical investigation, involves small

controlled clinical trials; and phase III, clinical trials, involves expanded trials of the drug in larger numbers of test subjects. FDA invites sponsors of commercial investigational new drugs (INDs) that represent important or modest therapeutic advances to participate in conferences at the end of phase II. These conferences focus on the results of phase I and II studies and the protocol to be followed during phase III. The objective of the conference is to speed up the drug's development during phase III by assuring the sponsor that phase III work will be acceptable to FDA. As of April 10, 1981, FDA had conducted end-of-phase II conferences with 24 drug firms and had invited amother 18 to participate in such conferences when they completed phase II clinical testing.

To determine how drug firms viewed the effectiveness of the conferences, we contacted 30 firms that either participated, or agreed to participate, in end-of-phase-II conferences. Those who participated characterized the conferences as excellent and helpful in identifying FDA's concerns. Officials from 29 of the 30 companies told us they strongly supported the conferences. Fourteen officials said FDA provided candid feedback on study design.

PRE-NDA SUBMISSION OF MANUFACTURING AND CONTROLS DATA HAS POTENTIAL TO HELP SPEED UP DRUG REVIEW, BUT FIRMS INFREQUENTLY DO SO

The manufacturing and controls data in an NDA include a description of a drug's components and composition, and the methods, facilities and controls for manufacturing, processing, and packaging the drug.

FDA has recognized that the manufacturing and controls reviews often add to the time taken to approve drugs. In December 1978, FDA therefore requested industry to submit the manufacturing and controls part of the NDA for drugs classified as important before submitting the full NDA. The purpose of this initiative is to allow an earlier chemist's review, so that this part of the NDA review would not delay final approval. Industry, however, has infrequently submitted its information early.

As of July 12, 1981, FDA had identified 37 firms eligible to submit manufacturing and controls data before submitting their fully completed NDAs. As of that date, 10 firms had submitted NDAs but had not presubmitted manufacturing and controls data. Only five firms had submitted such data before submitting an NDA.

Office of New Drug Evaluation officials believe sponsors often choose not to presubmit manufacturing and controls data because they do not make final decisions on the dosage form

for manufacturing the actual drug product until they are almost ready to submit the NDA. In addition, some sponsors may not be aware that they are sponsoring drugs for which early submission of these data is desired.

FDA's chemists advised us that presubmission can expedite the drug's review if the information submitted is complete and represents the firm's final decision on manufacturing and controls. If, however, the information is incomplete and is changed by the sponsor when the full NDA is submitted, FDA's chemists may have to duplicate much of their review.

PRIORITY REVIEW POLICY NEEDS TO BE DEFINED IN WRITING AND BETTER COMMUNICATED

To reduce processing time of important new drug applications, FDA established an initiative to give them "priority review." Priority review is intended to give important drugs special attention so that their applications are handled as rapidly as possible. FDA has not, however, defined this policy or the means for reviewers to implement it in writing. It has instead relied on oral communication. Many reviewers advised us that they have not understood how the priority review policy is to be implemented. Therefore, while some reviewers give important drugs high priority and make every effort to expedite their review, others do not and treat all NDAs on a first-come, first-served basis.

Although FDA has not developed a written policy on priority review requirements, the Deputy Associate Director for New Drug Evaluation said he was confident that reviewers have been told about the requirement.

We interviewed 41 chemists and medical officers who were responsible for reviewing important NDAs originally received in fiscal years 1979 and 1980. Thirty-three said they set their own priorities in determining the order in which they review pending NDAs. Fourteen told us they were unaware that important drugs were to be reviewed before others and that they review drugs in the order received regardless of therapeutic classification. Twenty-seven said they knew of the policy and that they review important drugs before other drugs.

Some reviewers also said they take additional steps to expedite the review of important drugs. For example, while FDA often waits until all reviewers have completed their reviews before notifying the drug firm of deficiencies--particularly if the deficiencies are major--some reviewers said they notify sponsors by telephone immediately when major deficiencies are found.

LACK OF CLEAR AGREEMENT ABOUT METHODS VALIDATION CONTINUES TO DELAY NDA APPROVALS

Despite FDA's initiative to speed up validation of analytical methods proposed by drug firms, validations are often delayed and are sometimes the sole factor delaying NDA approval. Methods validation involves an FDA laboratory verifying proposed test methods for ensuring the quality, strength, purity and identity of a drug. FDA has established a 45-day goal for performing this function.

As of July 14, 1981, FDA had completed methods validations on 14 of 41 important drugs submitted for review during fiscal years 1979 and 1980. Our analysis showed that methods validations averaged 182 days for the 14 important NDAs. None of the 14 were validated within 45 days. One method was validated in 47 days and another in 62 days. Time required to validate methods in the remaining 12 NDAs ranged from 104 to 411 days.

In December 1980, FDA published a study of deficiencies found in analyzing 105 letters in which it informed sponsors that their NDAs were not approvable. These NDAs were submitted during 1977 and 1978. This study showed that 59 (56 percent) of the 105 NDAs were deficient in methods validation.

While this study indicates that sponsors were not submitting the information FDA considered necessary to validate analytical methods, we found that FDA was also partly responsible

for this situation. An FDA validating laboratory branch chief told us, for example, that FDA review chemists often fail to send the information required to validate testing methods to the FDA laboratory. He said the review chemists either are not aware of what the laboratory chemist requires for a validation or do not agree with the requirement. Therefore, he felt that review chemists do not always assure themselves that the data submitted by industry are complete before submitting them to the laboratory for validation.

FDA has recognized the need to clarify its requirements for methods validation. On March 6, 1981, FDA established a task force to develop guidelines to address (1) what the Bureau of Drugs should expect from methods validation, (2) what information industry should submit as a part of its methods validation data, (3) what kinds of products require methods validation, and (4) what information the review chemists should send to the validating laboratory.

The guidelines were to have been ready for Bureau of Drugs review by September 1, 1981. However, on September 1, 1981 the task force chairman told us that the target date had not been met. He said a revised target of October 1, 1981 had been set and that he expects to have the draft guidelines ready for bureau review at that time.

BIOPHARMACEUTICAL REVIEWS
CONTINUE TO BE DELAYED

Efforts to speed up the reviews of the Division of Biopharmaceutics, which reviews such things as the rate of dissolution of a drug in the blood, have not been totally successful.

FDA officials told us that biopharmaceutical reviews are delayed because (1) biopharmaceutical studies are not consolidated into a single section of the NDA, (2) data requirements are not adequately communicated to NDA sponsors, and (3) many requests for biopharmaceutical reviews are not made until late in the NDA review. FDA also recognized that poor coordination existed between biopharmaceutics reviewers and other FDA reviewers of NDA material.

Based on an analysis of NDA reviews in 1977, the Division of Biopharmaceutics found that its reviews were often delayed because relevant studies were scattered through various sections of the NDA and were sent to the division in a piecemeal fashion by FDA review divisions. The analysis also showed that reviews were delayed by the need to clarify information submitted or the need to request additional studies from the sponsor.

Another factor which has delayed biopharmaceutical reviews is the untimely request for these reviews by the Office of New Drug Evaluation. For all important drugs

received in fiscal years 1979 and 1980 that had biopharmaceutical reviews, requests for these reviews were received an average of 133 days after receipt of the NDA.

According to Biopharmaceutics Division officials, one reason requests for biopharmaceutical reviews are delayed is that relevant studies are scattered throughout the NDA, and it therefore takes time for NDA reviewers in the Office of New Drug Evaluation to identify them before requesting a biopharmaceutical review.

STATISTICAL REVIEWS CONTINUE TO BE DELAYED

Efforts to speed up the reviews of the Division of Biometrics, which examines the statistical data in the NDA, have also not been totally successful. FDA recognized that statistical reviews have contributed to delays in NDA reviews and that improved coordination was needed between reviews conducted by medical officers and statisticians. To improve the coordination FDA included representatives of the Biometrics Division in monthly staff meetings to discuss problems they encountered and the priorities for reviewing various NDAs. Nevertheless, FDA officials told us that statistical reviews continue to be delayed because (1) data requirements of the statistician have not been adequately communicated to NDA sponsors and (2) statistical reviews are not requested in some cases until late in the NDA review phase.

To better inform drug companies of their requirements, division officials have worked with individual NDA sponsors and participated in various forums attended by industry representatives to explain the requirements. The division also developed draft guidelines to clarify data requirements and formatting needs for all sponsors and published a notice of availability for them for review and comment in the Federal Register in July 1980. The division is now revising these guidelines based on the public comments received. The Bureau of Drugs intends to make these guidelines available through the Federal Register when the NDA regulation revisions are issued.

In July 1980, the Associate Director for New Drug Evaluation issued a memorandum to all staff emphasizing FDA's 45-day target for statistical review requests. At the time of our review, it was too early to evaluate whether this clarifying memorandum had led to more timely requests. The proposed IND/NDA regulation revisions also are expected to provide for statistical data to be submitted in a separate section of the NDA. Division of Biometrics officials believe this will enable the medical officer to submit such data on a more timely basis to the division.

CONCLUSIONS AND RECOMMENDATIONS
TO THE SECRETARY OF HHS

FDA's efforts to expedite NDA review have achieved some success, but have not adequately addressed some problems which continue to delay the drug review. We are recommending that the Secretary direct the Commissioner of FDA to:

--Notify applicants individually when they have an IND that is a candidate for pre-NDA submission of manufacturing and controls data, but emphasize that they should presubmit these data only if the data are complete and in final form.

--Communicate in writing FDA's priority review requirements to all NDA reviewers. Such requirements should emphasize the need to (1) begin the review of important drugs ahead of others, (2) notify NDA sponsors of any deficiencies found in important NDAs immediately after the chemist, pharmacologist and medical officer have completed their reviews, and (3) request work from FDA support groups, such as validating laboratories, early in the review process.

--Decide what FDA will require for methods validation, communicate these requirements to NDA sponsors and all FDA review and laboratory chemists, and insure that these requirements are followed.

--Expedite FDA's review of the draft biopharmaceutical guidelines and make them available to NDA sponsors as soon as this review is completed.

--Establish a guideline for requesting biopharmaceutical studies and see that requests are made in a timely fashion.

--Make statistical guidelines available to all NDA sponsors as soon as they are completed.

--Insure that medical officers involve the Division of Biometrics statisticians early in the NDA review process.

FDA'S EFFORTS TO REWRITE THE IND/NDA REGULATIONS

As early as March 1978, the Commissioner of FDA expressed the agency's intention to rewrite its regulations on INDs and NDAs. The Director, Bureau of Drugs, in a public statement in December, 1980, said that the proposed revisions of the IND/NDA regulations are undoubtedly the most important activity in the IND/NDA area during the 1980s. Yet, as of August 1981 a draft of the regulations had not been released for public comment. FDA has advised us that a draft of the revised NDA regulations should be published by March 1982 and that these regulations will probably not become final for at least 2 more yers.

A draft of the revised IND regulations is not expected to be published for comments until October 1982.

To determine the types of changes likely to be made in the IND/NDA process, we interviewed cognizant Bureau of Drugs officials to obtain their reactions to a number of suggestions for speeding up the drug review process made by various organizations and individuals. On the basis of these interviews, it appears that FDA is considering some changes that should help improve the efficiency of the drug review process, including:

--Tailoring applications to FDA's different functional review units.

--Eliminating the requirement that companies submit detailed, individual case reports with each NDA.

--Decreasing the number of supplements that will have to be filed by industry and reviewed by FDA.

--Making greater use of postmarket surveillance studies as a condition for new drug approval.

--Eliminating the requirement for industry to provide FDA with some reports which would decrease the volume of paper flowing to FDA and free reviewers to perform other tasks.

--Improving coordination efforts among FDA's functional review groups.

--Allowing manufacturers more opportunity to voluntarily withdraw previously approved NDAs without fear that vital data would be disclosed to competitors. This would free FDA from review and recordkeeping requirements.

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Other suggestions have been made that FDA apparently has considered and rejected. We believe that some of these could similarly help to speed up the drug review process. These suggestions include:

--Improving procedures to ensure that questions arising during the review process are promptly communicated to the applicant.

--Developing procedures to clarify when previously reviewed data would have to be re-reviewed by FDA.

--Accepting foreign clinical studies that fully meet U.S. statutory requirements without requiring extensive additional U.S. testing.

--Holding mandatory conferences with applicants before granting any extension of the 180 day statutory limit for NDA review.

It is difficult to determine the extent to which the changes that FDA is considering will speed up the drug approval process. Many of the changes are procedural. The extent to which they will improve communication between industry and FDA is unknown and can only be assessed over time. FDA's willingness to accept foreign data seems to be increasing, but the agency will apparently continue to require some domestic verification of foreign studies. While we recognize that some verification may be necessary, we believe that the verification required should be kept to a minimum when foreign studies fully meet U.S. statutory requirements. In appropriate situations, FDA could require

postmarketing surveillance after approval rather than extensive, additional U.S. testing.

According to the Associate Director for New Drug Evaluation, none of the changes being considered will revolutionize the IND and NDA process nor are they expected to cause a dramatic decrease in the time required for NDA approval. FDA advised us, however, that it expects proposed regulation revisions to cut several months to a year or more off the average 7 year period from the beginning of human testing to approval of a new drug for marketing. FDA further advised us that the Commissioner will be evaluating the drug review process to determine whether additional managerial improvements can be effected to improve the overall review and regulation of drugs.

RECOMMENDATION TO THE SECRETARY OF HHS

Because of the importance attributed to the IND/NDA rewrite and the time which this effort has already taken, we are recommending that the Secretary direct the Commissioner of FDA to prepare a report to you, Mr. Chairman, detailing each change it has made or will make to speed up the drug approval process and estimating the amount of review time the change has saved or is expected to save.

The report should also contain information on the extent to which individual reviewers are accepting or rejecting foreign data submitted in support of NDAs and the specific reasons for rejections. The report should contain a timetable for FDA action indicating specifically when FDA intends to implement any planned action. The report should be issued by the end of calendar year 1981.

PROPOSED POLICY CHANGES MAY SPEED UP REVIEW OF INNOVATIVE DRUGS BUT DELAY GENERIC DRUG REVIEW

In addition to the initiatives discussed, FDA is considering changing the requirements and handling of post 1962 generic drugs--duplicates of innovative drugs already approved and marketed for public consumption. This change would (1) reduce the extent of industry testing and FDA review of drugs whose equivalents have already undergone effectiveness and safety approval by FDA and (2) consolidate the review of generic drugs under one division. If this is accomplished, FDA believes additional industry and FDA scientific personnel will be made available to review and approve--at a faster rate--drugs offering new therapeutic advances. This change is also intended to speed up the review of generic drugs, which are generally made available to the consumer at less cost than the innovator drug.

We believe that, while the change may speed the review of important drugs, faster review of generic drugs may not result because generics now processed by FDA's Office of New Drug Evaluation will be transferred to another Bureau of Drugs division which has a large backlog of unapproved applications. If additional reviewers can be found within the agency to assist with the increased workload delays in reviewing generic drugs may not occur. We believe that implementing this proposed policy change requires close scrutiny by the Office of the Commissioner to assure that unexpected adverse impacts are minimized.

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Mr. Chairman, this concludes my statement. We will be pleased to answer any questions you or other members of the Subcommittee may have.

APPENDIX

NDA APPROVALS AND PROCESSING TIMES FOR FDA DIVISIONS

AVERAGE FDA PROCESSING TIME

	FY 1976-1977		FY 1979-1980		
	NDA's approved as of 3/31/78	Months required for approval	NDA's approved as of 3/31/81	Months required for approval	Difference in approval time (In months)
Divisions that increased drug approval time					
Cardio-renal drug products	5	10.4	5	16.2	+5.8
Neuropharmacological drug products	12	9.8	4	11.4	+1.6
Oncology and radiopharmaceutical drug produtcs	5	15.4	3	17.8	+2.4
Surgical-dental drug products	11	9.0	43	10.6	+1.6
	33		55		
Divisions that decreased drug approval time					
Metabolism-endocrine drug products	9	12.1	30	5.7	-6.4
Anti-infective drug products	18	13.8	14	11.6	-2.2
	27		44		

Mr. SCHEUER. Very good, and thank you very much for your very helpful testimony.

Your testimony indicates and that chart clearly indicates that FDA has made progress in reducing the review time for some of the drugs but for others this time period has actually increased. It has increased in the most important areas affecting the health of America, we feel in the field of medicine.

In the field of oncology, cancer, what specifically do you feel has produced these increase in approval times, this lengthening approval process in these very most critical areas?

Mr. DENSMORE. Part of the problem seems to be that three of the four divisions that have increased the review time during the 1979–1980 period reviewed approximately 71 percent of the original NDA's categorized as new molecular entities. In 1976 and 1977, they had been responsible for about 59 percent of them, so there was an increase in the number of NDA's in this category.

These NDA's are the most complex and time consuming to review. That's part of it.

Part of it also seems to be the heavy workload of the reviewers in these divisions and the fact that some supervisors do not delegate to the extent probably that they should. There is an insufficient number of clerical staff to do some of the work that has to be done, which takes away from the time of the reviewers.

So it's a combination of a lot of these things that seem to have entered into it.

Mr. SCHEUER. It seems to me that as America's health improves we're going to see a higher incidence of people who survive other debilitating illnesses and eventually are subject to heart attack and cancer. I suppose that the efforts of the medical profession and the pharmaceutical houses to produce drugs to meet these important areas are on an increase, so I presume the burden on the FDA to approve these drugs is going to increase.

What do you think they are going to have to do to get their act together to meet what, by every test of logic and experience, is going to be a permanently increasing load? It's not a temporary increase in the number of applications; I presume they can look forward to that for the indefinite future.

Do they have to change their system? Should they rely more on postmarketing surveillance? Should they rely more on their advisory committees? What's the answer to the fact that they don't seem to be able to meet the burden or the challenge of approving drugs specifically aimed at cardio, renal and oncologic diseases, disabilities?

Mr. DENSMORE. This is certainly the area that the new Commissioner should give close scrutiny to. We feel there are some changes that can be made.

Let me ask Mr. Vieregge if he can give you some of the specifics that we might have, but it is certainly an area that the Commissioner should scrutinize.

Mr. VIEREGGE. Mr. Chairman, we have included a number of recommendations in our formal statement that you have and in the draft report, but in addition to those recommendations, let me point out just a few things FDA could consider. Among these, as Mr. Densmore indicated, is the additional scrutiny of the oper-

ations of these divisions. Since we didn't have the opportunity to go into these in depth I think it that certainly warrants additional consideration.

Beyond that, however, we believe that FDA could more aggressively manage the review process. Certainly as we pointed out in our report, there is an inconsistent adaptation or application of the priority review policies that the agency feels it has in place. It would seem to us that the burden of seeing that that policy is consistently applied falls upon the shoulders of the supervisors and management. Therefore, more aggressive supervision and management could do this.

Further, we think that the computer data base is unreliable, that this kind of data should be cleaned up, and to give FDA managers further insights into identifying problem areas.

In addition——

Mr. SCHEUER. It seems a little bit ridiculous, once they have the computer printout, that they have to go ahead and check it manually and find out that the manual process is more accurate. This is the automated system gone mad.

Please continue.

Mr. VIEREGGE. In addition, Mr. Chairman, we would suggest that FDA strive to change the mindset that appears to exist in the agency that perpetuates the notion that a 3- or 4-month delay in notifying a company of deficiencies is usual and acceptable. Each delay incrementally added together slows the drug-approval process.

Beyond that we think that FDA should eliminate the requirement that companies submit detailed volumes of individual case reports in support of an NDA. Rather, FDA should rely on summaries of the information.

Now this matter is being considered in the new drug application regulation revision, and it would be our suggestion, Mr. Chairman, that perhaps the Commission you appointed—the Congressional New Drug Review Commission—would find this and some other areas appropriate to take up and consider in its deliberations and interactions with the FDA.

Mr. SCHEUER. Have you had the opportunity to meet informally with that Commission?

Mr. VIEREGGE. No, sir, but we will have that privilege this coming month.

Mr. SCHEUER. I want to make sure there is good, informal communication between all of you.

Mr. VIEREGGE. One additional point if I may, Mr. Chairman:

In our previous report that you requested, that is the first drug approval process evaluation that we did, we made a recommendation that FDA did not accept. We recommended that in instances where industry is the major contributor to delays in the drug-approval process FDA should notify industry of those delays. In our judgment, this would sensitize a particular company to what it could do to straighten out things.

We don't propose that this be done across the board because it certainly would generate burdensome paperwork, but there must be some instances where there are glaring instances of these kinds

of delays and where that occurs, we think it would be appropriate to notify drug companies.

Mr. SCHEUER. Where that occurs at the instance of the pharmaceutical house?

Mr. VIEREGGE. Correct.

Mr. SCHEUER. I agree. The FDA is coming under a steady barrage of criticism from me and others. Where part of the problem cannot be fairly laid at their door, I think we ought to identify what the problem is, and all parties to the approval process are going to have to engage in a process of introspection and get their house in order.

And if that means the pharmaceutical companies have to improve their attentiveness and improve their response time, well, so be it. The FDA is not exclusively responsible for this problem. I find it a little difficult to understand why they would object to that proposal since it would make clear that all of the negligence or all of the delay cannot fairly be laid at their doorstep.

I'm very frustrated because I have a very long list of questions that time is not going to permit us to answer.

I'm going to ask the unanimous consent from all of the members to submit questions to you as soon as we get them all together, and I would also like to ask you whether you'd be willing to come back perhaps another day, after you have had a chance to meet with the Congressional Commission and perhaps after we've had a chance to review your recommendations with the FDA folks and find out which ones they seem to feel are workable and which ones they do not seem to feel make sense.

I would like to get your reaction to that, so if you have no objection, we will submit some further questions to you, and we may very well ask you to come back to help us process some of these problems.

Mr. DENSMORE. Fine, Mr. Chairman. We'd be pleased to do that.

Mr. SCHEUER. Wait a minute. I'm finished, but I still have my colleagues here who would like to ask some questions.

I would like to ask the ranking minority member, Mr. Carney of New York.

Mr. CARNEY. Thank you, Mr. Chairman. I'll be mercifully brief, knowing our calendar.

I have one question. You know, if you build a better mousetrap the world will beat a path to your door. Now it's obvious that other countries can get drugs out and into the marketplace faster than the United States has, based on its past performances.

Have you evaluated the systems that are used in Western Europe where they have the capability of doing that, and have you done a comparative analysis to our system here as opposed to their system?

Mr. DENSMORE. Yes, sir, we have. Not in this particular job but on the prior report that we issued, Dr. Grant visited several of these countries and maybe he can respond to that question for you and tell you which countries he visited, and go into whatever detail you want on that.

Dr. GRANT. We visited nine countries and developed a report trying to compare some of their systems with ours, and those are written in our report which is dated May 1980 and which reflected

some of our thinking in regard to what we saw in some of those countries, and comparing their system with ours.

There are many pro's and con's that one could discuss and we could spend a long time doing that. There are really no easy solutions, no easy answers. But the systems that are used in some of the countries that we visited such as those in Western Europe are, to some extent, quite dissimilar from ours.

And we felt at the time we visited and spoke with many of the people there, including Government officials and pharmacologists, that some of the systems they used appeared to be somewhat better than some of the things we do here.

On the other hand, one must admit there are different reasons for doing things in those countries than we have here. They have different political systems, different pressures which make for a different kind of a system. It's not very easy to just say that this is better than the other one.

But it is all embodied in our report which was rendered as I say last year.

Mr. CARNEY. As a followup to that report has there been any activity generated from it from the FDA?

That question perhaps should be asked of the next panel of witnesses, but have you seen that?

Dr. GRANT. Well, I think that perhaps the only way we can answer that is by only pointing out what Mr. Densmore has already stated, that there has been some improvement in the speed with which the FDA has proceeded with its drug review process, at least in some areas. Whether one can attribute that to our last report and action taken on that or not, I'm not sure, but at least we have seen some improvement.

Mr. CARNEY. As a personal opinion do you see the worthiness of taking some of the differences between the agencies in charge in other countries and applying it here in the United States?

Dr. GRANT. Well, I think just as other countries have some things that they possibly can learn from us, I think we can learn some things from other countries, too.

Mr. CARNEY. Thank you very much, Doctor.

I yield to my colleague from California.

Mr. BROWN. Mr. Densmore, do you have any specific information about the drug that we were considering earlier this morning with regard to its status?

Dr. GRANT. Mr. Brown, I do have some information on it although I would assume it would be better coming from the FDA. But it is my understanding that Newport Pharmaceuticals has been attempting to have this drug approved in this country for aperiod of about 11 years now for various purposes. I know it is under active review at the present time by FDA for this particular purpose.

It is my understanding that action was taken at a recent meeting of FDA's advisory committee to approve Isoprinisine but that approval was subject to FDA's reviewing the statistical data concerning the drug, and I believe that it is that question that is really holding up, more than any other, its approval.

FDA's review thus far, as I understand it, of the statistical information would indicate some problem in their minds and that's what they are really taking a good look at at the present time.

But I'm sure that FDA is in a better position to answer that.

Mr. BROWN. We'll go into that further with them.

Mr. Densmore, with regard to the situation in other countries, I seem to recall from the earlier report, and I haven't refreshed my memory on this, that one of the factors in the more rapid approval of new drug applications in some countries such as England may have been a superior postmarketing surveillance. Am I correct in this?

Mr. DENSMORE. Yes, sir.

Mr. BROWN. As I indicated earlier, we have had some general discussions within the committee at a few hearings with regard to the possible improvement in comprehensive or medical health information systems which should include as a component some aspects at least of postmarketing surveillance of drugs.

My question is, Do you see any reason why, given a technological capability to have more comprehensive health information systems and more adequate postmarketing surveillance systems, that we should be able to move in the direction of incorporating a broader range of data produced by this information system into the process in such a way as to expedite the approval process?

Mr. DENSMORE. Yes, sir, we'll agree with that. There could be greater use of postmarketing surveillance as an aid to speeding up the process. It could especially be done in those cases where there is a lot of information available from other countries. Where the drugs have been used for longer periods of time, information is available.

This would probably be another area that would be good for the new Drug Commission to discuss. There are many implications of course. We're changing our present system, placing more emphasis on postmarketing surveillance.

But that Commission could probably generate some useful discussion and reach some judgment in that area.

Dr. GRANT. Let me add something to this, Mr. Brown, if I may.

There is a good deal of attention being given to the question of postmarketing surveillance in this country because there are a lot of problems in making it more effective. One of the most significant problems—and here is one of the differences between the United States and many other countries—one of the real inhibitors of good postmarketing surveillance involves questions of malpractice. As long as you have the threat of litigation lying over the physician's head there will be some reluctance on his part to report adverse effects, and that is one of the major issues that is inhibiting postmarketing surveillance.

Mr. BROWN. From what you said, Mr. Densmore, apparently the information of FDA insofar as it's reflected in the computer operation shows a little bit of improvement. Is that right?

Mr. DENSMORE. Yes, sir.

Mr. BROWN. That's not uncommon. You run across that in a number of agencies. But it's agreed it's a generic problem and I think we need to be concerned with what can be done to improve

the transfer of more adequate technology to some of these agencies. And this is a concern that we have here also.

Ms. Schneider.

Ms. SCHNEIDER. I would like to pick up on that line of questioning. I don't quite understand how postmarketing surveillance seems to be effective in other countries, yet we here in the United States are concerned that there might be too many malpractices that would come as a result of this direction.

One of my reactions is, if we were to label and put a little yellow card, or whatever, in each drug or package that is sold, we could say very clearly that this may negatively impact your body or cause adverse reactions, and you're taking it essentially at your own risk.

I think it's pretty clear that in the sales of cigarettes it's clearly labeled that cigarette smoking may be hazardous to your health. And I haven't seen anyone who has contracted cancer attempt to sue the cigarette companies for, you know, respiratory diseases or any other kind of effects.

Maybe that's oversimplifying, but I don't quite understand, if it works in other places why couldn't it work here?

Dr. GRANT. For whatever reason, Ms. Schneider, it appears that we do live in a rather litigious climate in this country, perhaps more so than in some other countries. I don't think it is necessarily true to say that other countries feel that their postmarketing surveillance is very good. I think the question revolves around whether it is somewhat better than ours. There are some countries where it would appear to be better. And we reported on that back in our last review.

But I think that from what we have learned, it would appear to be true that the single most significant factor bearing upon the difficulties we have in getting adverse drug reaction reporting from physicians revolves around the threat of malpractice. There have been several studies done on this over many years, and this appears to be the single most important factor. There are some others, but that's the most important one.

Ms. SCHNEIDER. I have some other questions that relate to the FDA Expert Advisory Committees, and I wonder if you feel they're playing an important and valuable enough role.

Dr. GRANT. I don't think there's any question that there's a very important role for advisory committees in an agency such as the Food and Drug Administration. In our last report to which I have referred, we spent some time talking about the different systems used by other countries with advisory committees or, in some cases, in policymaking committees that some other countries have. And we have some question as to the manner by which advisory committees are structured and the way they were functioning here at FDA.

I think it's another subject that would be a very good one for the new Drug Review Commission established by Congress to look at.

For example, in the United Kingdom and in Sweden, advisory committees are in effect policymaking committees. In each country they consist of world recognized experts in the field who advise the government drug agency. By and large, their recommendations are generally accepted by the drug agency.

Now we operate in a different way in this country. I'm not necessarily saying that ours is better or that theirs is better. But I think that the differences are considerable between those countries and ours. And I think it's worthy of the new Drug Commission taking a look at it.

Ms. SCHNEIDER. Do you feel the FDA follows the recommendations frequently enough of these advisory committees?

Dr. GRANT. I'm not sure that I can answer that question as you've raised it, Ms. Schneider. But I don't think there's any question that the FDA does place a great deal of credence in what their advisory committees say. That doesn't mean to say they always follow them. But they they do pay a good deal of attention to what they say.

Ms. SCHNEIDER. Thank you very much.

Mr. BROWN. Committee counsel has some questions he would like to put.

Mr. SHACKNAI. Mr. Densmore, your study concluded that of the 34 percent of the drugs that were being approved by the Food and Drug Administration, they were being approved overall on a quicker basis in terms of actual months spent in the field.

I wonder, however, if you can tell us what the status is of the remaining 66 percent of the drugs which were not approved by the FDA.

Mr. DENSMORE. We have updated that information through July 31, 1981. As of July 31st, 1981, 28 of the 35 1976 and 1977 drugs had been approved; which is 80 percent. And 17 of the 41 drugs for the 1979–80 period had been approved; which is 41 percent.

Mr. SHACKNAI. What were your conclusions, then, in terms of the time spent in the approval process? Do they bear out your earlier findings, or do they in some way differ?

Mr. DENSMORE. The times increased a little bit as more time has gone by. For the 1976 and 1977 drugs, the time increased to 21 months from 15.5 months, and for the 1979-80 drugs it had increased from 8.9 months to an average of 10.6 months.

Mr. SHACKNAI. In terms of your finding that certain divisions of the Food and Drug Administration were actually increasing the time; specifically Mr. Scheuer raised the Cardio Renal Division and the Oncological Division; would your recent statistics also bear out the fact that they are taking more time, are they reducing time, or what exactly is the situation?

Mr. VIEREGGE. Mr. Shacknai, in looking at just the two divisions you talked about, it's safe to say that those times are significantly increasing. For example, for fiscal year 1976 drugs—and it must be understood here that we can no longer use the comparison when we go beyond the update; but using that comparative analysis we were seeing that the Cardio-Renal Division had approved 24 percent of its drugs in 10.4 months as of March 31, 1978. When we take that out to July 31, 1981, which is somewhere between 4 years 10 months and 5 years 10 months, we find that Cardio-Renal moved to 60 percent of those drugs approved, and their time went from 10.4 months to 25.4 months of FDA time. So what that tells me is that approved time will necessarily increase over time.

Now let me take that to 1979, which is the post-speedup period, if you will. What you see is Cardio-Renal had 21 percent of its drugs

approved, with an average of 17.5 months of FDA processing time. The update of that information shows that with an additional 4 months they approved 37 percent: that's going from 21 percent to 37 percent, and the average processing time went from 17.5 months to 18.4 months.

If you want to hear about oncology, I can bring those figures up, too.

Mr. SHACKNAI. Just generally, would you agree that it's taking more time now than when the information was originally compiled?

Mr. VIEREGGE. The time will lengthen; yes, sir.

Mr. CARNEY. May I pursue that a little further?

I can appreciate what counsel is trying to bring out, following up on matters that the subcommittee chairman also questioned about.

There's something that I have on my mind. You've identified that the timeframe has stretched out. But have we identified why? Is it because of the bureaucracy or is it because to do the proper research, since the drugs are becoming more complex, the identity of contradictions and the application of the drugs have now become harder and harder to find and don't show up in studies for longer periods of time? Or is it because we have advanced so far in the science of pharmacology, we know so much more, that it takes that much longer to identify the reactions to the intake of drugs in the body? Or is it simply that the bureaucracy is poorly managed, undermanned, or whatever?

Identifying that the timeframe has increased is one thing, but the "why" is what we're trying to get at.

Mr. VIEREGGE. Mr. Carney, your point is well taken. There is no simple answer to that question. It is a combination of factors.

Our report indicates that, in our judgment, some management type things can be done which will reduce some of this approval time. It won't necessarily override the changing technological aspects that you raised. However, in our judgment this time probably can be brought down.

Let me give you one example. In looking at the raw data on the unapproved drug applications what you see is that cardiorenal and oncology drugs, in a number of instances, show as much as 27 months of FDA time with zero months of industry time. There are a number of reasons for that. I don't know what they are specifically. It's for that reason that we said FDA should take a look at those dimensions to determine if there aren't some improvements that can be made.

Mr. CARNEY. I think that's precisely what this committee is trying to do, to stimulate that, and make corrections where necessary, whether it be through legislation or just through prodding of a Federal agency.

Mr. Chairman, I have no other questions of the witnesses.

Mr. SCHEUER. Well, thank you very, very much. We very much appreciate your coming here and your excellent and responsive testimony. We'll be sending you some questions, I'm sure, in writing. And we are also planning, probably planning on asking you to come back here some time in the next month or two, if you'll be willing to do that.

We thank you very, very much.

All right. We'll now hear from a very key player in this continuing scenario, Hon. Dr. Arthur Hull Hayes, the new Commissioner of the Food and Drug Administration.

Dr. Hayes, we welcome you here this morning. We're very grateful to you for coming up.

We received your somewhat amended testimony yesterday afternoon. We're very grateful that you took the trouble to make the additional contributions to your testimony, which we found very impressive and very encouraging.

Time is really too short to analyze your testimony as you would like. I am sure, in addition to the questions we'll be asking of you, we'll have additional questions in writing. And, as we discussed with the GAO folks, we may want to impose on your courtesy and patience and ask you to come back in another month or two to clarify any issues needing to be clarified.

As I say, I apologize for the fact that having had your testimony for well under 24 hours we haven't been able to give it the very thoughtful attention that it deserves.

Now your testimony will be printed in full in the record. So we'll leave it to you as to whether you want to read it, which you are perfectly well able to do, or whether you would simply like to chat with us informally, and then after that we'll have some questions for you.

So please proceed at will, and accept our thanks for coming up.

STATEMENT OF HON. ARTHUR HULL HAYES, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY GERALD F. MEYER, ASSOCIATE COMMISSIONER FOR MANAGEMENT AND OPERATIONS; DR. J. RICHARD CROUT, DIRECTOR, BUREAU OF DRUGS; DR. MARION J. FINKEL, ASSOCIATE DIRECTOR FOR NEW DRUG EVALUATION, BUREAU OF DRUGS, AND THOMAS SCARLETT, CHIEF COUNSEL, FOOD AND DRUG DIVISION

Dr. HAYES. With your permission, Mr. Chairman, we have submitted my full statement for the record. I have a summary statement that I think highlights some of the points that are of obvious importance to you and to us that perhaps I might read, and then be very happy to respond to your questions.

Mr. SCHEUER. Very well.

Dr. HAYES. As I think you know, Mr. Chairman, I have had an abiding interest in the Food and Drug Administration's drug approval process throughout most of my professional life. As a clinical pharmacologist who has conducted investigations of new drugs before accepting the position of Commissioner, I have been sensitive to and at times critical of the time it takes to bring important new drugs from the manufacturers' laboratories to the pharmacy shelves. As Commissioner, I have pledged to review carefully the FDA's new drug evaluation process and regulatory requirements to make them more efficient, flexible, and sound. The goal is clear: That safe and effective drugs get on the market with reasonable speed and without unnecessary regulatory requirements.

As one who proudly displays one of the pens used to sign into enactment the 1962 Kefauver-Harris amendments to the Federal Food, Drug, and Cosmetic Act, I understand their significance to drug regulation in this country. The therapeutic armamentarium of medicine today contains an array of drugs that are more rational, better understood, and more accurately labeled than were drugs on the marketplace before the 1962 drug amendments. The 1962 requirement for adequate and well-controlled clinical trials has revolutionized the quality of clinical trials and of drugs coming to the marketplace.

In the almost 20 years since those amendments were enacted, an extensive evolution in science and medicine has changed the development, testing, approval, and marketing of new drugs. Evolution brings new ideas, new opportunities, new scientific understanding and expectations, and new problems and new solutions. We see this in the regulation of drugs just as in other sectors of science and technology. Doctors, patients, the pharmaceutical industry, and indeed the Congress itself all expect the standards for drug approval to keep pace with scientific evolution.

Changes in science, technology, and public policy require continual review and updating of the regulatory process. The drug approval requirements need to be addressed in light of criticisms and the current thrust for regulatory reform. Today I want to describe FDA's program to help us reach this goal.

While the agency has over the past several years embarked on a variety of efforts to improve and streamline its drug approval process, I am committed now to the most thorough review of the intricate and complex details of the entire evaluation and approval process since the enactment of the Kefauver-Harris amendments in 1962.

On September 9, I announced the formation of a 21-member task force for the review and improvement of the drug approval process. The members are from the Food and Drug Administration and other components of Health and Human Services, and I will serve as chairman. The group has been formed to take a fresh look at the entire drug approval process and to recommend policy, regulatory, legislative, and management changes to improve the process without lessening FDA's concern for the safety and effectiveness of drugs.

The task force will go beyond past efforts and address major policy issues such as the criteria for new drug approval, the role of advisory committees and the deregulation of early phases of clinical research. The mandate of the task force is to develop an integrated plan for improving the new drug review process, including policy, regulatory, and legislative proposals for consideration by the administration and the public.

The task force will solicit views from a variety of sources including foreign drug regulatory agencies, industry, professional and consumer groups, and the Commission on the Federal Drug Approval Process. I have directed the task force to submit its recommendations by March 19, 1982; though, as I point out to you, Mr. Chairman, as recommendations are reached and decisions made as this process is going on, they will be implemented as quickly as possible.

Also, Mr. Chairman, I wish to commend you and Congressman Gore for your initiative in establishing the Commission on the Federal Drug Approval Process. The Commission, chaired by Dr. McMahon, and on which senior FDA staff serve as liaison members, will provide another but equally important forum for discussion on how the drug approval process can be improved.

I assure you that our task force will study carefully all of the recommendations of the Commission, with the intention of adopting those recommendations that will move us closer to the goal we all seek.

When I arrived at FDA last spring, I found that improvement of the drug review process has been a priority activity of the agency for some time, and that some improvements have been realized. One major focus of these improvement efforts has been and is on steadily strengthening the management of the review system and the reviewing staff; the second major focus has been on drug development by the industry.

Past administrations have instituted a series of procedural changes within FDA to allow it to identify important new drugs promptly and to manage them through the investigational and premarketing phases to assure that they do not languish from insufficient attention by their sponsors or by FDA. The agency has also established internal operating goals to reduce the in-house processing times for new drug applications.

The agency has also taken a number of other steps to cut down unnecessary delays in approval time. These include establishing goals to reduce, over a 3-year period, FDA processing time on new drug applications by 25 percent for drugs that represent important or even modest therapeutic gains, and 15 percent for all other drugs; increasing the monitoring of in-house evaluation processes, with emphasis on applications for drugs that offer important or modest therapeutic advances, and establishing guidelines on the procedures and standards to be used in the review of applications.

A major advancement involved the installation of a system of new drug classification. Under this system, using six chemical classes and three classes of therapeutic potential, the Bureau of Drugs classifies IND's and NDA's by chemical type with respect to therapeutic potential.

Another major initiative has been the publication of guidelines for clinical studies for 28 classes of drugs in humans. Committees of the Pharmaceutical Manufacturers Association participated in the original drafting of these guidelines, as did FDA's scientific advisory committees in their subsequent review.

The agency has also encouraged more communication between FDA and the pharmaceutical industry during the IND phase. This, I believe, has clearly helped in moving drugs more quickly and smoothly toward approval.

Beginning in the mid-1970's, we requested that companies meet with FDA at the end of phase II on all drugs considered significant or modest medical advances. A similar meeting was requested prior to the submission of an NDA. More recently, the agency has invited the submission of manufacturing and control aspects of NDA's for important new drugs before the remainder of the NDA is completed.

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These conferences during the development of drugs, and the early submission of manufacturing and control data have served to identify problem areas before the full NDA is submitted and significantly aided the agency's review. I believe it is important to continue these efforts and that even greater time savings can be achieved by open communication approaches of this type.

While I understand there is a widely believed idea that FDA does not accept, for purposes of new drug approval, clinical trials conducted outside the United States, I can assure you that this is not the case. FDA always has had a policy of accepting foreign studies when those studies meet the same standards of quality as we require of domestic studies, and this policy has been in FDA's regulations since 1975. The current debate is not so much over the acceptance of foreign studies but over whether a drug should be approved in the United States solely on the basis of foreign data without any domestic data whatsoever. This is a controversial suggestion that raises a number of policy concerns but will be considered in the context of the Commissioner's task force review. I expect this issue will also be debated by the McMahon Commission.

We have met with many foreign drug regulatory authorities, both at international meetings and in bilateral exchange visits, to discuss the exchange of information on regulatory matters and to educate each other on mutual approaches to controversial decisions. These exchanges include the tripartite meeting involving the United Kingdom, Canada, and the United States; the First International Conference on Drug Registration Authorities held in Annapolis, Md. in October 1980 under the joint sponsorship of FDA and WHO, and bilateral exchanges with many countries throughout the world.

Each country will benefit if drug officials in various nations understand each other and encourage a harmonious approach to drug evaluation so that duplicative and unnecessary studies are eliminated and science is treated similarly throughout the world.

I am pleased to have inherited as Commissioner an agency actively interested in the problem of orphan drugs. This has laid a foundation for public consideration of this issue, and we intend to continue exploring how each of the many parties can best contribute to the marketing of these drugs. We are pleased that the Pharmaceutical Manufacturers Association has formed an Orphan Drug Commission, and I have indicated to PMA that FDA is ready to assist the Commission in any way possible. I have discussed this important issue with PMA representatives and the meeting between them and myself is now being scheduled to coordinate our efforts.

The GAO in its May 28, 1980, report concluded that approval takes a long time and that the process could be improved. While FDA did not concur with many of the specific conclusions reached by GAO, it did agree that improvements to the review process were needed. In fact, FDA has already implemented several of the GAO recommendations.

We have recently received a draft GAO report on another shorter GAO review of our drug approval process. We intend to comment on the draft, and I assure you the agency will give serious consideration to the recommendations of the final report.

We are happy to note, however, that this recent GAO report did say that the FDA has substantially exceeded its goal in reducing approval time for important new drugs.

So far, Mr. Chairman, we have spoken about much of what has already taken place and is continuing to evolve. However, these efforts are not enough, and we are in the midst of some exciting new activities.

I have committed a significant share of the Bureau of Drugs regulations writing resources to redraft its regulations to improve the new drug evaluation process and to refine its policies and practices for reviewing and processing IND's and NDA's.

The Department plans to publish proposed revised NDA regulations in the Federal Register this coming spring. Proposed revisions to the IND regulations are scheduled for similar publication late next fall.

I have approved the agency's plans to use guidelines extensively to add flexibility for easier accommodation of innovation in the entire drug investigation, review, and approval process. They will aid manufacturers in the submissions for bioavailability and bioequivalence studies, stability studies, preclinical studies, manufacturing data, and statistical analyses of safety and effectiveness data. These will supplement the existing guidelines relating to clinical studies.

Strategies under consideration include reducing FDA's involvement in the conduct and monitoring of the early stages of clinical investigation and the possible elimination of the requirement that manufacturers submit certain protocols, data, and reports during these stages. Experience has shown that the industry and FDA have sometimes devoted far too much attention to drugs that are discarded very early during their investigation.

I also believe it is important to explore the possibility that more responsibility can be shifted to local institutional review boards, (IRB's), to lessen the degree of FDA monitoring and control of the early phases of clinical studies. One of the options being suggested is to increase the role of IRB's in reviewing, approving and monitoring early phase investigations.

Earlier this month we published in the Federal Register a notice seeking information from IRB's, IRB members and others to help us determine whether the IRB's are capable of and willing to assume the additional responsibilities, and whether any increased role of IRB's would subsequently reduce administrative burdens while ensuring adequate protection to the public. When completed, I will share with you the results and our analysis of this survey.

We are strongly considering elimination of the general requirement for applicants to submit all case report forms in NDA's, often amounting to dozens or even hundreds of volumes. Under this concept, the NDA would contain, instead, detailed tables constructed from the data in the case report forms. Case report forms for selected studies might still be necessary only to allow spot checking of the data. These types of proposed changes will surely evoke considerable controversy, and there is great need to structure and evaluate them carefully.

In closing, I would like to briefly comment on a few other opportunities for changing and influencing the new drug-approval process.

The current requirement for substantial evidence of effectiveness on the basis of adequate, well controlled clinical trials can delay approval of a new drug that represents a major therapeutic advance for a life-threatening or severely debilitating ailment. In such situations, provisional approval on the basis of a standard of significant evidence of effectiveness with adequate evidence of safety might allow earlier approval of such a drug. We are currently studying this issue.

As you know, bills are pending in the Congress that will extend the patent life of new drugs. I support this proposed legislation. I believe that it is among the initiatives that will help to encourage innovative research and the development and marketing of important new drugs. I hope it will have an impact on the orphan drug issue where, in some cases, an extended patent life may make the difference in deciding whether to devote resources to the development of a drug of low commercial interest.

The determination of a drug's potential benefits, its potential risks, and the balancing of the benefits against the risks involve extensive evaluation of data and complex scientific judgments. These evaluations can only be done by reviewers who are medically well trained, logical, and are able to apply critical thinking. The data available are never sufficient or absolutely clear-cut. The reviewer must be able to ask the important questions and pick out the crucial data.

Drug evaluation carries with it the dual responsibility to assure protection of the public from drugs which are unsafe or ineffective while simultaneously assuring that new drugs which offer therapeutic gains over currently marketed drugs are identified and brought to the market as expeditiously as possible. I am sensitive to this need and to striking an appropriate balance between the adequate scientific testing of new drugs, the therapeutic needs of patients, and the business incentives of manufacturers in a free enterprise economy.

I want to underscore that in considering changes in the regulations and administration of the evaluation process, I do not want to suggest that we diminish or compromise the bedrock foundation of drug regulation in the United States. One of the important tenets of the way we practice medicine in this country is that physicians and other health professionals and the people they serve have a right to expect that the drugs they receive are safe, effective, properly labeled, and manufactured with the highest standards of quality. FDA has the responsibility to assure that its regulatory program accomplishes this and that it is also efficient and works to the benefit of the public.

In this country, as in much of the world, the pharmaceutical industry and the academic scientific community share the responsibility for rational drug development. As regulators, we at the FDA have a responsibility to make requirements clear, to review data carefully, to advise sponsors on the submission of investigational and new drug applications, and to conduct our review process efficiently and in the public interest. But the ultimate responsibility

for performance of good studies and expeditious submittal of data is with the drug industry. The quality of the application submitted to FDA still remains the single most important factor influencing the speed of review and approval of the drug.

Our goals are clear. The task is difficult. I am impressed that the agency has made progress in the past, but we can and I promise will do more in the future. I personally look forward to significant accomplishments and the satisfaction that they will bring.

Mr. Chairman, this concludes my summary statement. My colleagues and I will be pleased to answer any questions you may have.

[The prepared statement of Dr. Hayes follows:]

STATEMENT BY

ARTHUR HULL HAYES, JR., M.D.

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

INTRODUCTION

Mr. Chairman, let me begin my remarks this morning by saying it is a pleasure to be here, as I have had an abiding interest in the Food and Drug Administration's (FDA) drug approval process throughout most of my professional life. As a clinical pharmacologist who has conducted studies of new drugs before accepting the position of Commissioner, I have been sensitive to and at times critical of the time it takes to bring important new drugs from the manufacturers' laboratories to the pharmacy shelves. As Commissioner, I have pledged to review carefully the FDA's new drug evaluation process and regulatory requirements to make them sounder, more efficient, and more flexible. The goal is clear: that safe and effective drugs get on the market with reasonable speed and without unnecessary requirements.

I want to underscore safe and effective because, in modernizing the regulations and administration of the evaluation process, I do not want to suggest that we diminish or compromise the bedrock foundation of drug regulation in the United States. One of the important tenets of the way we practice medicine in the United States is that physicians and other health professionals and the people they serve have a right to expect that the drugs they receive are safe, effective, properly labeled, and manufactured with the highest standards of quality. The Food and Drug Administration has the responsibility to assure that its regulatory processes for oversight of the drug market are efficient and work to the benefit of the public.

As one who proudly displays one of the pens used to sign into law the 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, I understand their significance to drug regulation in this country. The therapeutic armamentarium of medicine today contains an array of drugs that are more rational, better understood, and more accurately labeled than were drugs on the marketplace before the 1962 Drug Amendments. The 1962 requirement for adequate and well-controlled clinical trials has revolutionized the quality of clinical trials and of drugs coming to the marketplace. In the almost 20 years since those Amendments were enacted, an extensive evolution in science and medicine has changed the development, testing, approval, and marketing of new drugs.

Evolution brings new ideas, new opportunities, new scientific understanding and expectations, and new problems and new solutions. We see this in the regulation of drugs just as in other sectors of science and technology. Doctors, patients, the pharmaceutical industry, and, I am sure, the Congress expects the standards for drug approval to keep pace with scientific evolution. Evolution also brings new responsibility to both Government and industry.

Evolution and changes in science and technology require review and continual updating of the regulatory process. The drug approval requirements need to be addressed in light of criticisms and current mandate for regulatory reform. Today I want to describe the current and planned activities to help us reach this goal. While the Agency has over the past several years undertaken a variety of efforts to improve and streamline its drug approval process, we are committed now to the most thorough review of the intricate and complex details of the

entire evaluation and approval process since the enactment of the Kefauver-Harris Amendments in 1962.

A major revision of the regulations relating to new drugs is underway in the Agency. The current regulations governing investigational new drugs (IND), and new drug application (NDA) approval are basically unchanged since they were promulgated in 1963. This rewrite is intended to deal solely with the modernization of those regulations. However, our overall considerations go much further. We are also considering the need for new legislation, for new scientific guidelines and for updating existing ones, and for changes in the administrative and managerial policies and procedures by which the applications are evaluated.

To accomplish this overall review, I recently appointed a 21-member Task Force for the Review and Improvement of the Drug Approval Process. The Task Force, to consist of members from FDA and other agencies within the Department of Health and Human Services, has been formed to take a "fresh look" at the entire drug approval process and to recommend those changes that will improve the process without lessening FDA's concern for safety and effectiveness of drugs.

My purpose during this effort is to assure that the review is as thorough as it can be, that all avenues for improvements have been explored, and that our part of the system is in tune with the times and operates as efficiently as possible.

We are looking at the new drug evaluation process from beginning to end, and not only from within the Agency; rather, we are soliciting broad participation from industry, professional associations, consumer

and patient groups, and the Congress. Some participation has already come in the form of the debates and comments on drug legislation previously considered by the Congress in 1978 and 1979. Suggestions have come from a public hearing in November 1979 on the IND/NDA (investigational new drug exemption/new drug application) rewrite concept document. We have had the benefit of close scrutiny of the review process by the Secretary's Review Panel on New Drug Evaluation in 1977 and two in-depth reviews by the General Accounting Office in 1980 and 1981. We have received citizens' petitions from the pharmaceutical industry, from professional groups and from private citizens making specific suggestions for change. The President's Task Force on Regulatory Relief, chaired by Vice President Bush, has sent us comments. And of course we are looking forward to the report and recommendations of the Commission on the Federal Drug Approval Process under Dr. F. Gilbert McMahon's leadership.

The people within the Agency know a lot about the drug review process and some of the things that can be done to make it better, but they are the first to agree that innovative ideas are needed from outside the Agency. We are eager for thoughtful suggestions on how to improve the process.

In this country, as in much of the world, the pharmaceutical industry and the academic scientific community share the responsibility for rational drug development. As regulators, we at the FDA have a responsibility to make requirements clear, to review data carefully, to advise sponsors on the submission of investigational and new drug applications, and to conduct our review process efficiently and in the public interest. But the ultimate

responsibility for performance of good studies and expeditious submittal of data is with the drug industry. The quality of the application submitted to FDA remains the single most important factor influencing the speed of review and approval of the drug.

COMPLEXITIES OF ISSUE

Concept of Safety

At this point, I would like to discuss the concept of safety as it applies to drugs and to dispel the common mistaken notion that a drug can be inherently safe.

Although we talk of a drug as being safe, no drug is absolutely safe. Every pharmacologically active drug can cause harm--undesirable effects--which can be extensions of the drug's beneficial pharmacological properties, or can be unrelated. An essential part of drug development is to determine what the adverse effects are, their frequency, and in which group of patients they are more likely to occur.

The decision whether to approve a drug is made for a specific use of the drug and involves a complex balancing of the potential risks of the drug against the potential benefits. For a drug of clear but limited potential benefit, for example, a drug for a stuffy nose, the acceptable potential risks are far less than the risks acceptable for a drug useful in treating a life-threatening infection. When a drug is to be used over many years, as for high blood pressure, certain kinds of adverse effects, e.g., nausea or diarrhea, may not be accceptable although they can be acceptable when a drug is used for a short time. If a drug offers no potential benefit to patients, then no risk is

warranted. This is only common sense and is the basis for the 1962 Amendments to the law which require a showing of effectiveness, in addition to the previous requirement for safety.

An essential purpose of clinical testing of a drug before market approval is to detect adverse effects that are frequent and serious. However, detection of relatively rare adverse effects cannot and should not be a goal of premarket testing, because of the very large number of patients required. An adverse reaction with a frequency of 1 in 1,000 patients is considered uncommon, but if it is medically serious, it clearly assumes public health importance if the drug will be used by millions of people. The reporting of adverse events in patients who receive the drug after marketing is a useful way of detecting and determining the incidence of rare and infrequent adverse reactions. The monitoring of adverse reactions is well-accepted today as an essential scientific endeavor that complements the pre-marketing evaluation of a drug.

The benefit/risk ratio for a drug may change after marketing when the drug is widely used. New adverse effects may be discovered, or particular groups of patients may be identified who are more or less likely to develop adverse reactions. The drug also may be found to be effective for new uses other than those studied before marketing. When these new discoveries are made, the labeling of the drug may need

revision. Occasionally, if a very serious reaction or risk is discovered, the benefit/risk balance may tip in favor of removing the drug from the market.

A drug is approved for marketing with professional labeling which includes a description of the drug; the uses for which it has been shown safe and effective; contraindications, warnings and precautions; dosage recommendations; and the adverse effects of the drug. Part of the process of drug development and review involves defining the patient populations most likely to benefit from the drug and the patients, e.g., those with kidney disease, who are most likely to have certain adverse effects. When the benefit/risk consideration is close, carefully prepared drug labeling, with specific cautions and limitations on use, or an explicit description of the patients who might benefit, may be sufficient to minimize patient risk and may be an alternative to more stringent regulatory action, i.e, not approving the drug at all.

The determination of a drug's potential benefits, its potential risks, and the balancing of the benefits against the risks involve extensive evaluation of data and complex scientific judgments. These evaluations can only be done by reviewers who are scientifically well-trained, and logical, and who can apply critical thinking. They must maintain a healthy, scientific skepticism to counterbalance the natural enthusiasm that a drug with potential medical usefulness engenders when it first becomes known. They must strive to develop a balanced point of view, with sensitivity to both the benefits of the new drug and its potential risks.

Different people will inevitably make different judgments on scientific as well as other matters. This is part of the reason that a drug is evaluated at FDA by a team of reviewers, with different scientific backgrounds and experience and at different administrative levels. In this way the professional judgments of any one individual are not given undue importance. The advice and judgment of experts outside FDA, and from the public as well, contribute to the decisions made.

Differences in the Testing of Drugs

The extent of effectiveness testing required for a drug depends in part on the degree of effectiveness of the drug. Very effective drugs, such as penicillin for pneumococcal pneumonia, need limited testing and rigorous observation on few patients.

Drugs of marginal or borderline effectiveness require large numbers of patients and elaborate statistical analyses in order to demonstrate their effectiveness. Drugs that have relatively clear-cut objective criteria of effectiveness, such as a change in a laboratory test value, are easier to study than those that cause subtle subjective changes. Sometimes, the relevance of a change in a blood chemical like cholesterol, to a long-term disease process like coronary artery disease, may not be clear; this relationship is not required to be studied in the short-term testing done before approval of a drug for marketing. Some answers require many years of observation of patients, and the expectation of clinical benefit may justify making the drug available before the answers are known.

The amount of testing, to a lesser extent, is related to the size of the population with the disease or in whom the drug will be used after

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marketing. For a rare disease, few patients are available for testing. For a common disorder, such as high blood pressure, the potential population exposed to the drug is very large and heterogeneous. Therefore, more information is required about a new drug's side effects, its interaction with other drugs commonly used in the same patients, and its safe and effective use in patients with other diseases likely to co-exist with high blood pressure, such as cardiac disease. For any drug, a careful study of a small group of patients is more likely to yield usable information than a large and careless study.

Sometimes a new drug, which is a member of a class of drugs already extensively studied, may be tested mainly to determine its similarities and its differences compared to others in the class and will not require the same extensive testing used to evaluate earlier drugs in the class.

The extent of both clinical and animal testing required before marketing also varies with the disease, the length of therapy that will be required, the size of the population at risk, and the degree of effectiveness demonstrated during early testing. The need for animal carcinogenicity studies, animal reproduction studies, human studies in special groups, such as people with liver disease or children, will vary with each drug, although a certain nucleus of information is essential for all drugs before marketing.

The FDA has the obligation to make its requirements flexible and appropriate to the particular drug at hand. To aid in accomplishing this, the Agency has for some years published guidelines for the clinical evaluation of many classes of drugs. These guidelines are

used widely by the industry not only in the United States but throughout the world.

Scientific Evolution

As basic science and understanding of the human body evolve, fruitful areas for drug development appear. Recent exciting elucidations of the existence and role of small polypeptides, such as the endorphins, in body and brain homeostasis have already led to the development and beginning of testing of some of these substances and analogues. Because of a scarcity of these peptides, FDA has shown flexibility in tailoring the extent of animal testing that is required.

As physiological mechanisms are better elucidated, drugs can be developed to affect a specific enzyme or body regulatory system. Factors governing the discovery and development of new drugs are complex, and FDA must keep its regulatory requirements sensible and appropriate. By the same token, as the technology develops for detecting or predicting harmful effects, such as carcinogenicity, FDA will need to adjust regulatory requirements to ensure that the harmful effects are detected.

New scientific technologies, like techniques for synthesis of hormones or proteins using recombinant DNA, were recently assessed in an Agency study performed to help plan for adjustments needed in the regulatory process. FDA must also react to this revolution in science by attracting scientists competent in new scientific fields. The Agency recognizes the need to provide opportunity to its scientific

staff for professional development through education, experience, and communication with other scientific professionals. We need to maintain and update our laboratories' scientific equipment and procedures so that FDA can continue to be a contributing and respected part of the scientific community; we are continually striving to maintain this position.

REVIEW OF NEW DRUG APPROVAL PROCESS

Let me briefly summarize FDA's procedures and requirements for the investigation, review, and approval of new drugs for marketing in the United States.

To initiate studies in humans a manufacturer must submit to FDA an investigational new drug (IND) application. This application contains the relevant chemical, pharmacological, and toxicological information, plus a protocol for the initial study to be conducted in humans. The investigator may proceed with the study after a 30-day waiting period which allows FDA time for initial review and to raise questions on safety that need resolution before study in humans begins. The study must be reviewed and monitored by an institutional review board (IRB) to protect the safety of the participants and to assure their rights. It is particularly essential that human subjects give their consent voluntarily after being properly informed of the nature of the study.

As the investigation proceeds, the manufacturer keeps FDA informed of new studies including animal studies, makes progress reports, and is responsible for alerting FDA and clinical investigators immediately of unforeseen serious side effects or injuries. This research is conducted in three phases: Phase I, in which the pharmacological

effects and possible toxicity are evaluated in a small number of volunteers or patients; Phase II, in which the drug is carefully evaluated in a small population of patients for its effectiveness and short-term side effects in controlled clinical trials; and Phase III, in which greater numbers of patients are employed and broader information is gathered to provide the basis for its proper use by physicians.

When the research and development phase is completed, the manufacturer gathers together the results of all studies and submits them to FDA in a new drug application (NDA). This application is reviewed in detail by a team of reviewers, including a physician, a pharmacologist- toxicologist, a chemist, and often a biopharmaceutics expert and a statistician. The application is often also discussed before an advisory committee or it may be reviewed by outside consultants. Based on these reviews, a decision is made for approval or nonapproval of the NDA. A decision for approval for marketing includes approval of drug labeling, which will provide necessary information to the physician and which is based upon the data submitted in the NDA. The Federal Food, Drug, and Cosmetic Act provides 180 days within which to make this decision. It should be noted that this 180-day provision was enacted long before the scientific evolution I mentioned moments ago. More data of ever greater sophistications on ever more complex drugs are required to be reviewed under this same time period established years ago.

The NDA review determines whether the drug meets the statutory standards for marketing: firstly, that the drug has been shown to be safe for use under its proposed labeling conditions. Secondly, there

must be substantial evidence that the drug is effective for its proposed indications. Substantial evidence is defined by statute to mean evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved. Thirdly, the manufacturing methods, facilities and controls used in producing the drug must be shown to be adequate to preserve its identity, strength, quality and purity.

Considering the complexity of the drug investigation, the poor quality of many submissions, and the number of factors to be considered in the review process, it is not surprising that an NDA is rarely approved within the 180-day period provided in the statute. An NDA is seldom approved without the need for further data, discussion of scientific problems, and for many drugs, presentation to an advisory committee.

Clearly, the quality of the data and its presentation is the most significant factor contributing to ease of review and more rapid decision on the approvability or nonapprovability of an NDA. We have worked extensively with our advisory committees, the industry and its trade associations to develop guidelines for clinical studies. A similar set of guidelines is now under development for the submission of manufacturing and control information. We continue to refine and improve the guidelines and to meet with manufacturers individually insofar as our resources permit.

The Agency maintains a cooperative and open policy in meeting with industry. Our administrative procedural regulations set forth specific

guidance and requirements for Agency personnel in meetings with outside parties, and also establish guidance for those outside of Government who wish to meet with an Agency official.

FDA has a responsibility to meet with all segments of the public to promote the objectives of the laws that we administer. I am firmly convinced and committed to the need for constructive dialogue between government scientists and professionals and their outside counterparts. These exchanges in a nonadversarial atmosphere are essential to mutual understanding and progress in resolving today's technological issues. Such meetings must be open and the discussions recorded to ensure propriety.

Workload of Reviewing Staff

The drug investigation and review process is scientifically complex and involves issues at the forefront of medicine and science. The challenges to the Agency and its advisors are immense. One cannot but be impressed that the basic new drug review staff--consisting of the approximately 77 physicians, 50 chemists, 36 pharmacologists, and 40 Consumer Safety Officers--handles annually 1,000 new IND's, 175-200 original NDA's, 4,000 supplements, many thousands of amendments, 30-45 advisory committee meetings, and many hundreds of meetings with industry. These people also handle the continuing review of the effectiveness of drugs marketed before 1962, when the effectiveness requirement was added to the law. In addition, these scientists monitor published and unpublished reports of new adverse reaction information on marketed drugs and take appropriate action based on the new information. They are also involved in frequent updating of the labeling for marketed drugs to provide physicians with

the latest information. These same individuals also must deal with the scientific issues that arise from the current massive review for safety and effectiveness of all over-the-counter drugs now marketed. Lastly, they have to handle large numbers of Freedom of Information requests, Congressional inquiries, and other correspondence. Adding to the complexities and sometimes contributing to delays in the deliberative process of new drug review are other factors:

--/ The extensive use of advisory committees and outside consultants;

-- Mounting numbers of consumer and industry petitions;

-- Requests for hearings;

-- Law suits challenging Agency decisions on drugs;

-- Investigations by the GAO and others; and

-- Oversight by Congress.

While we believe these pursuits are healthy and reinforce the need for sound, well-documented, and reasoned decisions, they are costly to Agency resources.

International Differences

Drug development in the United States today is part of an increasingly international undertaking. Most major pharmaceutical manufacturers are multinational and seek world marketing of their products. In the last two decades major companies began to focus heavily on international markets as well as the United States in their drug development strategy. This shift in drug development has occurred for a number of reasons: growth of research capabilities in Europe and Japan, fewer

regulatory restraints on clinical research in most other countries, and, in some cases, economic and marketing considerations.

In this country public attitudes toward drug approval are reflected in our legal requirements for safety and effectiveness, stringent requirements for protection of human subjects that include institutional review and informed consent, and are influenced by the nature of our medical care system. Our strict standards mandated by law and regulation may slow approvals of drugs as compared to some other nations, but they increase the availability of high-quality information for decisionmaking and of high quality medicines.

Approval of a drug in the United States can be essentially a universal license; as a practical matter, FDA decisions strongly influence regulatory agencies in many countries of the world. There are occasions when drugs are put through the United States system with the intent of marketing them solely in other nations. This reflects the strength and prestige of our system.

We hear commonly the criticisms that other countries approve more drugs, approve different drugs, and approve them faster than or before FDA. These criticisms which also have come from the General Accounting Office, have been lumped under the basic rubric "drug lag." We have agreed with many of them, resulting in some of the efforts discussed in my statement today.

Although detailed information is scanty for most countries, drug approvals clearly take longer in countries with developed regulatory systems which independently evaluate information on a drug. These countries also tend to have well-developed pharmaceutical industries,

highly developed scientific technology, and high standards of medical care.

Among these countries, the array of marketed drugs varies, fashions in therapeutics differ, and the drugs perceived by the industry or by physicians to be worthy of marketing are not the same. It is unreasonable to expect that any single nation will always be first in approving what are considered to be important new drugs for the market.

If one identified a subpopulation of new chemical entities which were approved by all or most of the advanced countries during the last decade, I would venture to say that it would show that no country had a particular advantage in approving all of them first.

The country where a drug is introduced first is the result of a complex series of decisions involving such factors as the country where the molecule was first identified, the research resources available to the discoverer, the disease for which the drug is intended, the differences in research costs between a multinational corporation's research facilities in different countries of the world, economic incentives including the value of currency and tax structures, and finally the differences in the regulatory requirements among the developed countries. While all of the developed countries require that drugs be shown to be safe and effective before marketing, their regulatory programs differ. Many countries do not regulate investigational phases at all; some countries regulate only the later stages of investigation; and only a few other countries regulate the

full spectrum of investigation, from initial use in man until marketing approval. Thus, in looking at the lengths of time between first submission of some kind of application to various drug regulatory agencies and their final approval, one must take into account the different scope of review imposed by each of those systems.

These comparisons, however, must consider not just the length of time it takes the scientists and physicians to review the reports and data in the applications but also the broader construction of national policies of government. In the United States we take pride in an open system of government. This system includes decisionmaking on the basis of an administrative record of the evaluation of any application, open public meetings of advisory committees with opportunity for public participation and comment, a Freedom of Information Act that provides access to much of the information upon which the drug is evaluated and approved for marketing, and frequent and proper oversight of the regulatory process. This stands in stark contrast with most other countries where after staff review, applications are presented to a single body empowered to make decisions. Often their recommendations are so influential that the official agency, which meets in private, routinely accepts them and the decisions are not appealable or are subject only to limited appeal.

We have to protect the openness and accountability of our current system, but at the same time we continually seek changes to make it function as efficiently and sensibly as possible.

EARLIER ACHIEVEMENTS AND CURRENT EFFORTS

Earlier Achievements

Improvement of the drug review process has been a priority activity of the Agency for many years. One major focus of these improvement efforts has been and will continue to be on better management of the review system and the reviewing staff; the other focus has been on drug development by the industry. Innovations in our internal procedures during the past 8 years have included:

-- reorganization of the reviewing divisions into drug class groups;
-- the establishment of a comprehensive advisory committee system;
-- the development of an automated management information system for tracking applications and reviews;
-- the establishment of a classification system for drugs based on therapeutic importance and a system of priority review; and
-- the development of a set of internal review guidelines containing time goals, and meetings with management to follow progress.

We have instituted a series of procedural changes to allow us to identify important new drugs promptly and to manage them through the investigational and premarketing phases to assure that they do not languish from insufficient attention by their sponsors or by FDA. We have established goals for ourselves to reduce our own in-house processing times for new drug applications in order that we make better and quicker decisions.

We have taken a number of other steps to cut down unnecessary delays in approval time. These include the following:

-- Establishing goals under the Department's Management Initiative Tracking System (MITS) and Operational Management System (OMS) to reduce, over a 3-year period, FDA processing time on new drug applications by 25 percent for drugs that represent important or modest therapeutic gains, and 15 percent for all other drugs.

-- To monitor further the progress of in-house evaluation processes, administrative rounds are conducted each month with key New Drug Evaluation staff and division supervisors. Special attention is paid to applications for drugs that offer important or modest therapeutic advances to assure that unnecessary delays or problems do not impede the review process.

-- Guidelines for the evaluation of IND's and NDA's by Bureau physicians and scientists have been developed to establish common procedures and standards for the reviews of applications.

-- Drugs with sufficient therapeutic potential are handled with special attention and with continued contact with the sponsor. As an example, the FDA urged Abbott Laboratories to submit the NDA for valproic acid a year before the firm had planned to do so. The entire review of the drug, including its evaluation by our Peripheral and Central Nervous System Drugs Advisory Committee, was completed and the drug was approved in 160 days.

A major advancement involved the installation of a system of new drug classification. This procedure has proved useful both in assessing historical trends in drug availability and in considering how to deploy FDA resources to facilitate evaluation of important new drugs and minimize the time required to review NDA's for these new entities. Under this system, using six chemical classes and three classes of therapeutic potential, the Bureau of Drugs classifies IND's and NDA's by chemical type with respect to therapeutic potential.

One benefit of the classification system is that it provides a sound method of evaluating both the innovating performance of the industry and the efficiency of the approval process.

Other initiatives aimed at the pharmaceutical industry have included the following:

-- FDA has invited the Pharmaceutical Manufacturers Association (PMA) to propose standard formats and data presentations for various drug categories. PMA has developed and given to FDA guidelines for data submission.

-- FDA with the help of the scientific community and industry has developed and made available to the pharmaceutical industry guidelines for designing studies in testing 28 classes of drugs in humans. When used by industry, clinical studies submitted to us are more likely to be soundly designed.

Some of our other activities are directed toward the pharmaceutical industry. We have encouraged closer, more formalized communication between FDA and the pharmaceutical industry; this has clearly helped in moving drugs more quickly and smoothly toward approval.

I believe that by proper planning and timely meetings with manufacturers to explain the needs and requirements for new drug application approval, we can improve the track record for decisions on new drug applications. Scientific and regulatory problems inevitably arise during the research and development phase. It is longstanding policy to meet with manufacturers concerning these problems, to review protocols on request before important studies are undertaken, and to review the results of certain studies, particularly in the areas of chemistry and toxicology, even before a new drug application is submitted. These meetings will continue.

In 1976, we formalized our policy for initiating conferences with drug firms to discuss the results of early testing of promising new drugs as a means of accelerating the availability of drugs that offered important therapeutic gains. Drug firms producing drugs not considered important new drugs can also request conferences to obtain specific guidance on their product development.

FDA's objective in these meetings is to ensure that the sponsor knows early in the research process what evidence is required to demonstrate its drug's safety and effectiveness. Conferences are held with sponsors of IND's for drugs that are new molecular entities representing important or modest therapeutic gains at the conclusion of Phase II of the investigational process. The results of the completed

effectiveness trials are discussed to reach agreement as to what additional studies will be necessary in Phase III in order to submit a new drug application.

Beginning in 1978 we requested that companies submit during the final phase of clinical testing data on the manufacturing control aspects of the chemistry portion of NDA's for important new drugs before the clinical testing was completed. Previously, such information was submitted with an NDA after clinical testing had been completed. Early submission of manufacturing control data can speed up the approval of important new drugs by identifying problem areas before a formal NDA is submitted. We hope in the future to achieve more time savings by this type of approach.

We are trying to dispel the widely repeated statement that FDA does not accept, for purposes of new drug approval, clinical trials conducted outside the United States. FDA always has had a policy of accepting foreign studies when those studies meet the same standards of quality as we require of domestic studies. As early as the mid-1960's, a few years after passage of the 1962 Drug Amendments to the Federal Food, Drug, and Cosmetic Act, FDA approved some NDA's for safety and effectiveness largely on the basis of foreign data.

Because the purpose of clinical trials of a drug is to evaluate safety and effectiveness under conditions of use that resemble those in our own health care system, we normally require that at least some studies on a new drug be conducted in the United States.

To clarify our policy, in 1975 the Agency published regulations establishing the basis upon which data from foreign clinical research can be used in support of a new drug application. These regulations state that adequate and well-controlled foreign trials supported by case records will be accepted on the same basis as such trials conducted in the United States. These trials must be conducted according to the ethical standards of the Declaration of Helsinki or of the laws of the country of origin, whichever provides the greater protection to human participants.

FDA is currently making extensive efforts to state our policies in public forums, speeches, and industry meetings. A recent major speech was "Acceptance of Non-United States Data By The Food and Drug Administration - Current Position," presented by Marion J. Finkel, M.D. at the 82nd annual meeting of the American Society for Clinical Pharmacology and Therapeutics, March 19, 1981, New Orleans, Louisiana. My task force on Drug Approval will also be taking a fresh look at our current policy and make their recommendations in March of 1982.

Another of FDA's earlier achievements has been to provide a reasonable and efficient administrative mechanism for approval of generic products. The concept of abbreviated new drug applications (ANDA) is important. A full new drug application containing all of the required data for safety and effectiveness would impose a barrier to manufacturers who wish to market a drug product in competition with a pioneer drug for which the patent has expired. FDA has eased this burden for products that duplicate effective pre-1962 approved drugs by allowing submission of abbreviated new drug applications. Clinical and

preclinical data are not required in ANDA's because safety and effectiveness have already been demonstrated as part of the DESI project. ANDA's eliminate unnecessary human experimentation and expensive, time-consuming clinical trials to obtain safety and effectiveness data on drugs already well studied. Only manufacturing data and evidence of bioavailability are required.

Duplicates of post-1962 approved drug products also may be approved without new clinical studies through a "Paper" NDA, i.e., an NDA relying entirely on published scientific articles for evidence of safety and effectiveness where adequate data are available. Since such published data are not always available, and even when they are, considerable resources are expended by industry in compiling the information and by FDA in reviewing it. The Agency is planning to issue regulations to permit many members of this class of drug to be approvable on the basis of abbreviated new drug applications (ANDA's) which will be less resource consuming for both industry and FDA.

Of the total number of NDA's approved during the last 5-year period (1976-1980), 20 percent were for new molecular entities and represented 92 new drugs not previously available in the United Stated.

In evaluating these 92 new drugs, FDA considered 48 of them (52 percent) to offer important or modest therapeutic gains over existing therapies. This is a clear sign of a healthy climate in new drug research.

On the other hand, only 17 percent of the total approvals represented drugs offering therapeutic gains over already marketed drugs, while 83 percent were approvals of drugs offering little or no gain. In

examining this group further, one notes that almost 52 percent of all the applications approved were for Type 5-C drugs, i.e., drugs already marketed by other firms.

The Agency's efforts to date have been fundamentally successful. In the face of an ever-increasing workload and a more open, complex review process, the scientific staff has more than doubled the number of reviews per reviewer in the past decade. In spite of this, FDA total review times for NDA's, which increased during the mid- to late-1970's, have been reduced substantially in the past year or so. We intend to make this trend continue.

International Cooperation

We have met with the drug regulatory authorities from many foreign countries, both at international meetings and in bilateral visits, to discuss information sharing and ways in which information may be exchanged. As a result, the FDA routinely sends information on its drug approvals and other major actions to the World Health Organization and to over fifty foreign countries.

Each country will benefit if Government officials in the field of drug regulatory science in various nations encourage a harmonious approach to drug evaluation so that greater understanding is achieved of each other's standards and decisionmaking processes.

The highly successful first International Conference of Drug Registration Authorities was an important first step in this process. In October 1980, FDA, in cooperation with the World Health Organization (WHO), hosted this conference for drug regulatory officials from all over the world. Dr. J. Richard Crout, Director of the Bureau of Drugs,

FDA, was chairperson of the steering committee and co-chairperson of the conference. The proceedings recently have been published.

The conferees discussed the potential gain from the sharing of accurate and timely information on important new safety concerns on specific marketed drugs. The participants also agreed to share information upon which the original drug approval actions were based (FDA Summary Bases of Approval were considered a model.) The sharing of such information ultimately could speed both the introduction of new drugs worldwide and the making of appropriate decisions on marketed drugs.

The conference set the stage for future informal, as well as formal, sharing of information and guidelines among the countries. This exchange cannot help but have a salutory effect. The challenge to each country, however, will be to maintain contacts with counterparts in foreign governments--notwithstanding turnover in personnel and changes affecting the bureaucratic locus or structure of each country's drug registration authority.

Another important challenge grows out of the discussion on harmonization. The group selected areas for potential harmonization in the new drug approval process. The first effort is to take part of the new drug application and attempt to develop a uniform format and content. This requires selecting the correct elements on which to focus--and in this, the role of the pharmaceutical industry looms large. It was decided that the World Health Organization (WHO) should take the lead in meeting with the pharmaceutical industry to solicit advice on the selection of the appropriate elements. The second area

relates to harmonization of technical aspects of guidelines, including guidelines for clinical trials, preclinical trials, preclinical studies, etc. There was much discussion of priority-setting and cooperation with industry internationally and nationally, especially in the guideline area. The delegates, of course, recognized the reality and necessity of national legislation governing the new drug approval process.

All of the recommendations were made in an atmosphere of cooperation and enthusiasm generated during the session. Clearly, now that the meeting is over, FDA and WHO and the other countries must aggressively pursue the conference recommendations. The group plans future meetings and in the meantime, the types of activities under consideration will be the subject of continuing informal communication.

I would now like to turn to two other important issues related to the new drug approval process.

Validity of Data

Careless science and false preclinical and clinical research data submitted to us for review on some occasions have been a serious concern. The drug approval process depends upon truthful and accurate scientific research and on reliable data.

As a response to the discovery of fraudulent practices in preclinical testing laboratories, FDA's Bioresearch Monitoring Program was initiated in June 1977. The program, through investigations of preclinical and clinical studies, seeks to assure that drugs are approved for marketing on the basis of valid research data and that human test subjects involved in the research are adequately assured of their rights and safety.

Invalid or unreliable data mean that human research subjects were exposed to needless risk and that scarce scientific resources and time were wasted, if studies must be repeated. Furthermore, the entire population could be exposed to unnecessary risk if a drug were approved on the bases of data later found to be erroneous.

Orphan Drugs

The other issue is one which has been the subject of great concern to FDA, industry, and Congress. A group of drugs that has perhaps suffered more than any other in the drug development process has been "Orphan Drugs." The unavailability of drugs having low commercial interest, known as "orphan drugs," has been a public issue for several years. We have been concerned during these years about the problems of drugs which either (1) may be therapeutically useful for a small patient population but which have no commercial attractiveness because of the potentially limited distribution; or (2) may be useful for a large patient population but are not patentable, and thus, also, are of little commercial attractiveness.

Early this year, we testified before the House Subcommittee of Health and the Environment, Committee on Energy and Commerce, and discussed FDA's activity with orphan drugs.

An interagency Task Force on Significant Drugs of Limited Commercial Value was established in March 1978 under the leadership of Dr. Marion J. Finkel, Associate Director for New Drug Evaluation, Bureau of Drugs, FDA, and in its June 29, 1979 report presented a number of options for handling the problem of orphan drugs.

FDA has already proceeded towards increasing the availability of some of these drugs by compiling the available literature on them and/or seeking a drug sponsor to market the drug under an approved new drug application (NDA). FDA staff has met with clinical investigators studying orphan drugs to assist them in designing the kinds of studies needed to obtain marketing approval. The Agency has attempted to keep data requirements at a minimum, commensurate with the limited use and special benefit-risk considerations of these drugs, some of these drugs may offer great potential benefit in patients with a serious disease not otherwise treatable. FDA also has arranged for certain essential animal safety tests to be done by the National Cancer Institute or by FDA's National Center for Toxicological Research.

The National Institutes of Health (NIH) also has contributed to the effort by supporting considerable research on new drug through grants and contracts. For example, the drug development program at the national center institute (NCI) sponsors research on a broad array of drugs for the treatment of cancer. The anti-epileptic drug development program of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) also develops new therapies for patients with convulsive disorders. The National Institute on Drug Abuse (NIDA) has sponsored the development of drugs useful in the treatment of

narcotic addiction. The National Institutes of Health also has contributed to the development of drugs for, as examples, serious virus diseases, certain blood disorders, and gall stones. Not all of these studies are on drugs of little commercial value, but some are.

While progress is being made, many of us, including the Task Force, believe that more could be done. We recognize that some of the orphan drugs approved in recent years have taken a long time from their initial discovery to marketing. The pharmaceutical industry bears the responsibility for developing or not developing most orphans drugs; the PMA has recently formed a committee to study the issue.

Individual patients, meanwhile, can receive some of these orphan drugs under individual investigational new drug exemptions. I expect as we focus more attention on this problem, solutions will appear; FDA will continue to do what it can to be responsive to this need.

FDA Response To GAO Recommendations

The GAO in its report published on May 28, 1980, entitled FDA Drug Approval--A Lengthy Process that Delays the Availability of Important New Drugs, concluded that approval takes a long time and that the process could be improved. FDA did not concur with many of the specific conclusions reached by GAO, but does agree that improvements to the review process are needed and can be realized.

Over the past several years the Agency has given extensive attention to the policies, procedures, and management of the evaluation process. The Agency has implemented a number of initiatives to implement the GAO recommendations and has implemented other initiatives to improve the process. I have already discussed many of these achievements and will now only summarize our actions.

-- Under the Department's Management Initiative Tracking System (MITS), and Operational Managements System (OMS), the Agency has agreed to reduce over a 3-year period, our processing time on new drug applications by 25 percent for drugs that represent important or modest therapeutic gains, and 15 percent for all other drugs. FDA's action plan is on schedule.

-- The Agency has reiterated and clarified policy on the acceptance of data from foreign clinical studies in support of NDA's.

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-- The Agency is initiating a major revision of the IND/NDA regulations to streamline the review process and to eliminate any outmoded or unnecessary requirements to approval.

To streamline the review process, GAO recommended giving the industry timely feedback on deficiencies in NDA's and instances that are responsible for delaying approval of new drugs. The Department concurred with GAO's recommendation on the principle of feedback. FDA currently provides industry with feedback on deficiencies in NDA's during the review process through industry conferences, deficiency letters, and through detailed written responses when the review is completed.

We have recently received a draft GAO report of another shorter review of the drug approval process. We intend to comment on the draft and implement most, if not all of the recommendations.

SELECTED CURRENT ACTIVITIES

So far, we have spoken about much of what has already taken place and is continuing to evolve. However, we are in the midst of some exciting new activities.

IND/NDA Regulation Review

As touched on earlier, we have committed a significant share of the Bureau of Drugs resources to redraft its regulations to improve the new drug evaluation process and to refine its policies and practices for reviewing and processing IND's and NDA's. Task forces of the Bureau of Drugs personnel prepared concept papers suggesting revisions in the IND

and NDA regulations and the Agency held a public meeting on November 7, 1979, to discuss these concepts. We have also received many written comments. Drafts of the revised IND and NDA regulations have been prepared and are under review by a steering committee that includes Bureau of Drugs' management and representatives from the Commissioner's office, other Bureaus, and the Office of the General Counsel.

FDA plans to publish proposed revised NDA regulations in the Federal Register in FY 1982. Proposed revisions to the IND regulations are scheduled for publication in the Federal Register in FY 1983.

Guidelines

The Agency plans to expand the use guidelines to add flexibility for easier accommodation of innovation in the entire drug investigation, review, and approval process. They will supplement the regulations, which are structured to be succinct and broad.

In addition to the existing guidelines for performance of clinical studies, we will provide guidelines to aid manufacturers in the performance of bioavailability and bioequivalence studies, stability studies, and preclinical studies. We will provide guidelines for submission of data from each of these types of studies, as well as the submission of manufacturing information. Also, we will provide a statistical documentation guide for protocol development and NDA submission.

Regulatory Changes in Early Studies

Strategies under consideration for reducing regulation of early phase research include reducing FDA's involvement in the conduct and monitoring of the early stages of clinical investigation and the

possible elimination of the requirement that manufacturers submit certain protocols, data and reports during those stages. Experience has shown that the industry and FDA have sometimes devoted far too much attention to drugs that are discarded very early during their investigation.

We are exploring the possibility of shifting more responsibility to local Institutional Review Boards (IRBs) to lessen the degree of FDA monitoring and control of the early phases of clinical studies. One of the options being suggested is to increase the role of IRB's in reviewing, approving, and monitoring early phase investigations. Earlier this month, we published in the Federal Register a notice seeking information from IRB's and IRB members and others to help us determine whether the IRB's are capable of and willing to assume the additional responsibilities and whether the increased role of IRB's would subsequently reduce administrative burdens while ensuring adequate protection to the public. When completed, I will share with you the results and our analysis of this survey.

The current statute gives the Agency discretion in choosing a strategy to regulate investigational drugs. We believe extensive improvements can be made in the IND process through regulation, without statutory change.

Appeals

We have received a number of requests for specific procedures to appeal Agency decisions. Although a general procedure for appeals of decisions on IND's and NDA's is already contained in our procedural regulations, this procedure is apparently not as useful to industry as

it might be and there is a need for improvement. FDA is developing a system for appeals in the IND process to permit the rapid resolution of problems arising during the review. This is a difficult problem that is plagued by competing and sometimes intense views. We will publish as part of the NDA rewrite a proposal concerning appeals.

Case Report Forms

We are strongly considering elimination of the general requirement for applicants to submit all case report forms in NDA's (dozens to hundreds of volumes). Under this concept, the NDA would contain instead detailed tables constructed from the data in the case report forms. We may still need to require submission of case report forms for selected studies to allow spot checking of the data. These types of proposed changes may need further consideration and we will welcome all views.

International Activities

Plans are already well underway for the second International Conference of Drug Registration Authorities to be cosponsored by the World Health Organization and the Ministry of Health of Italy to be held in Rome in April 1982. There were 34 nations at the Annapolis Conference. We hope that word of the usefulness and accomplishment of that Conference will stimulate even more countries to attend the next one.

Communications with our colleagues in Great Britain and Canada through the Tripartite group continue with a high degree of activity, candor, and cooperation. We are continuing our communications and cooperation with many other countries in the world, including Australia, Brazil, Egypt, Israel, Japan, Nigeria, The People's Republic

of China, The Netherlands, and Sweden. While the nature and substance of our communications with each country may differ as a function of the interest and the development of its drug regulatory program, the one common theme is our mutual resolve to communicate and cooperate to assure safe and useful drugs for all our populations.

Post-Marketing Studies

FDA currently sometimes approves drugs with the condition that additional studies be conducted if it is in the interest of the public health. FDA has considered a proposal to codify a post-marketing studies requirement under which, as a condition for approval, an applicant may be required to conduct surveillance of the use of and experience with a drug product after it has been approved for marketing, or to carry out additional studies of the drug. The post-marketing studies requirement is based on the Agency's authority in the Act to require applicants to establish and maintain records and make reports.

Although we have imposed these requirements in the past, codification will define the circumstances in which this is appropriate. If long-term safety studies or studies in additional patient populations are carried out, we could make certain drugs available more rapidly than would be possible if the data were demanded before approval.

Orphan Drugs

The Agency is considering the modification of requirements for approval of significant new drugs for uncommon diseases, drugs which are usually of limited commercial attractiveness. Firms often will not develop such drugs because of a mistaken notion that the same amount of data

which is requested for a drug for widespread use will also be required for drugs of limited use. In fact, FDA tailors its requirements to the particular drug and disease, as I stated earlier in my testimony. We must remain sensitive to this need.

We recognize there is a great need in this area and we are doing all that we can to hasten the approval of these drugs. We are also aware that the Pharmaceutical Manufacturers Association has formed a Commission to identify orphan drugs and to make information on these drugs available to pharmaceutical firms.

Records and Reports

We have discussed the possibility that we will revise requirements for the maintenance of records to eliminate some reports now required during the first two years after approval of a drug. These changes will reduce significantly the record and report burdens on applicants following Agency approval of a drug.

Supplemental Applications

FDA proposes to eliminate many supplemental new drug applications now required for virtually any change in manufacturing or packaging. We have already published a final rule which has eliminated the submission of distributor supplements, which totaled 2,000 to 3,000 annually, thus eliminating a burden on industry and the Agency.

Post-1962 ANDA's

We are drafting also a regulation to extend the acceptability of ANDA's to include duplicates of most post-1962 approved drug products, thus eliminating unproductive repetition of drug investigations. We are on notice that such an action may be contested in the courts.

Commission on New Drug Approval Process

As I mentioned earlier, complementing the regulation rewrite and the efforts of the recently established FDA Task Force is the Commission on New Drug Approval Process, which you, Mr. Chairman, and Congressman Gore have sponsored, and on which FDA staff serve as liaison members. I am certain that through all of these efforts there will be a better appreciation by all, of the forces involved in drug development and evaluation.

While it is too early to speculate on the results of the Commission's review, I look forward to its completion. I can assure you that I will study its recommendations very carefully and will direct the FDA Task Force also to review the recommendations with the intent of acting on those that will move us closer to the goal we all seek.

OTHER OPPORTUNITIES FOR CHANGE

Change in Evidence Standard

In closing, I would like to briefly comment on two other opportunities for changing and influencing the new drug approval process. The current requirement for substantial evidence of effectiveness on the basis of adequate and well-controlled clinical trials may delay approval of a new drug that represents a major therapeutic advance for a life-threatening or severely debilitating ailment. In such situations provisional approval on the basis of a standard of significant evidence of effectiveness with adequate evidence of safety might allow earlier approval of the drug. We are currently studying this issue.

Patent Bills

As you know, bills are pending in the Congress that will extend the patent life of new drugs. I support this proposed legislation. I believe that it is among the initiatives that will help to encourage innovative research and the development and marketing of important new drugs. Hopefully, it will have an impact on the orphan drug issue where, in some cases, an extended patent life may make the difference in deciding whether to devote resources to the development of a drug of low commercial interest.

CONCLUSION

Drug evaluation carries with it the dual responsibility to assure protection of the public from drugs which are unsafe or ineffective while simultaneously assuring that new drugs which offer therapeutic gains over currently marketed drugs are identified and brought to the market as expeditiously as possible. FDA is sensitive to this need, striking an appropriate balance between the adequate scientific testing of new drugs, the therapeutic needs of patients, and the property rights of drug manufacturers. Mr. Chairman, your interest in this area has increased public awareness of this need.

Our goals are clear, the task is difficult, but we have made and are making progress. I personally look forward to significant accomplishments and the satisfactions that they will bring.

While this concludes my formal statement, my colleagues and I will be pleased to answer any questions.

Mr. SCHEUER. I want to express my gratitude to you for coming here today and testifying, Mr. Commissioner. We've had several meetings before. I am particularly grateful to you for your having assigned several members of your top staff to work informally with our Commission that Al Gore and I established, and I'm grateful that they're serving as ad hoc members. We very much value their contribution. I want to thank you for that. And I want to thank you for your cooperative attitude all the way down the line. We look forward with great pleasure to working with you.

You mention on page 20 of your testimony, you say in the last sentence of that paragraph that the system should work for the benefit of the public. Let me assure you that we share your concern. We are not trying to diminish the health prospects of the American public, we are trying to improve the health prospects of the American public.

We think that drug therapy is one of the most important elements of modern medicine, and we want safe and effective drugs to get to the American public faster. I don't know how I can encapsulate our goal more effectively than that.

We are absolutely committed to maintaining safety, to maintaining efficacy. But we think there are ways of getting drugs, especially drugs that are being used successfully all over the world for many, many years, more quickly to the American people, to save lives and to enhance the quality of life for hundreds of thousands, if not millions of Americans.

As far as I'm concerned, the interests of the pharmaceutical industry come second; the interests of the medical community come second; the interests of the bureaucrats at FDA come second; the interests of the politicians in Congress and public officials come second. We're all charged with producing the end result of benefiting the American people. Let me assure you that we totally join with you in that commitment.

I'm going to defer my questioning until after my colleagues have had a chance to ask you some questions.

Let me introduce the ranking minority member of our committee, Mr. Carney.

Mr. CARNEY. Thank you, Mr. Chairman.

Dr. Hayes, I certainly hope that your obvious enthusiasm turns out to be productive. Your take-charge attitude since you've become Commissioner will improve the role of the FDA.

I have a couple of questions that kind of come out of left field, perhaps from my ignorance of the FDA scheduling and priorities.

I would like to ask, first, how much time does the FDA spend on what I would consider over-the-counter drugs, new over-the-counter drugs, as opposed to therapeutic drugs requiring prescriptions, requiring that they be utilized only under a doctor's care?

Dr. HAYES. You mean in terms of resources or number of drugs or hours spent in reviewing?

Mr. CARNEY. Yes.

Dr. HAYES. Would you speak to that, Marion?

Dr. FINKEL. Well, there are very few new over-the-counter drugs, but we're currently involved in the procedure of reviewing the safety and effectiveness of those which are on the market. And panels of outside experts have found that, whereas many drugs are

safe and effective, there are some that need additional study in order to establish that.

We are just starting to receive data generated as a result of those new studies. And the same people who review the data for the prescription drugs also review the data for the over-the-counter drugs. So far it has only taken a fraction of their time; I would say no more than 10 percent. But this is expected to increase.

Mr. CARNEY. I'm confused. If a labeled over-the-counter drug that you see advertised on television is approved by the FDA, and a competitor comes along with a similar drug under a different label, a small change in it, like maybe a buffering agent for an aspirin-type drug or something like that, does that require the whole run of investigation?

Dr. FINKEL. No; the FDA's expert panels have written monographs, and the monographs are based upon ingredients in drugs. So if they say that aspirin is effective for headache, for example, anybody can then market aspirin for headache without doing any additional studies.

Mr. CARNEY. Thank you.

Dr. Hayes, in your testimony you said that since 1975 we have utilized foreign studies. And then you said that the current debate is not so much over the acceptance of foreign studies but over whether a drug should be approved in the United States solely on the basis of foreign data without any domestic data whatsoever.

Now, what does that mean? Do we accept foreign data exclusively and approve a drug?

Dr. HAYES. No; we do not at this time. We accept foreign data as part of the data to underwrite the safety and efficacy of a drug. And we have, even before 1975. The regulations were formalized at that time.

What we do not do, and about which there is a great deal of controversy, and an issue which we are addressing in our task force, as Dr. McMahon is in the Commission, is whether in fact there are times or reasons when a drug should be approved for use in the United States when all of the clinical research has been done outside this country; that is, that has never been studied by a physician in this country.

At first blush that seems like a very simple question. You say, well, if the criteria are good, then why do not you just accept the data? But I submit that it is more complex, and the issue is deeper than that, as those who have been involved will readily attest to, and as the Commission already has. And that is the following:

In this country we not only know what the standards are, because we set those, but we know the investigators, we know what institutional review boards are, we know how research is done in this country, we know the qualities of everything from medical training, pharmacologic training, and the like. In other countries we have no way to get this information. We are not allowed to inspect, to visit, to ask questions. Some countries will not let us see case report forms or even interview physicians; they refuse to be interviewed. So we have to take everything at their word.

In some cases this is fine: They are established investigators, and we know them. In other cases we have no such assurance. And, therefore, even though the data may seem to satisfy criteria, the

validity or the quality of the data is something that we have absolutely no check on. And there are many in this country, most especially many clinical investigators, who are concerned that the quality may not be the same, and that, therefore, the decision would be based upon a different kind, or a different quality of information.

There is also the problem, though it is tangential to this, that if indeed all data for a drug approval can come from outside the country, that there will be relatively less testing of drugs in this country, at least it is certainly possible and may be based upon economic and other issues. And I think it is important that a viable, energetic, innovative segment of our research in this country be on new drugs.

I am not suggesting the FDA is trying to promote drug research in this country or that we are there to subsidize clinical investigators. The substantive issues on the validity and the quality of data are most important. But the other cannot be divorced from it. And I think it would be a disaster if we ever came to the position where it was not possible to do adequate clinical investigations in this country, and then the need would arise, perhaps, when a drug could not be studied for that very reason.

Mr. CARNEY. Could you give me an example of where, by utilizing data from a foreign source, we have eliminated a step, or steps, in the process of putting a drug on the market in the United States since 1975?

Dr. FINKEL. Well, there is a drug for the treatment of bronchial asthma called beclomethasone. It's given by inhalation. It was approved a few years ago, and the vast majority of the clinical studies were done overseas. The U.S. studies were just very small and supplemental.

More recently, just in 1978, or perhaps 1977, there was a drug called Tagamet, which is very widely used for treatment of ulcers and other gastric intestinal disorders. And the vast majority of studies were performed overseas.

We have other examples. I could give you a whole list, if you are really interested.

Mr. CARNEY. How long did the American studies take, when we did utilize that type of data?

Dr. FINKEL. Well, they didn't take very long. The Tagamet studies were actually two small studies, and the Beclomethasone studies were also very small.

Because we waited for those studies to be finished, it did extend the time until the drug reached the market. If the firms had anticipated a little bit better the time when they would want to submit an application to the FDA, they could have started a year earlier with those U.S. studies.

Mr. CARNEY. Well, how long did it take for the drugs to get on the market after we initiated procedures?

Dr. FINKEL. Well, the Tagamet new drug application was approved within, I think it was, about 14 months. We would have liked to have approved it earlier. But the reason for the longer period was that in animal studies done in this country there appeared to be an increase in tumors which had to be evaluated by us and our advisory committee.

As far as the Beclomethasone, that was approved reasonably rapidly; I just don't know how long.

Dr. HAYES. Another point, too, Congressman, when we are talking about foreign data, that I think is important, and I think physicians and clinical investigators would echo this: It is not uncommon for the treatment of certain diseases or conditions pharmacologically to be different in different countries.

I will give you an example from my own professional experience, and that is the treatment of essential hypertension in the United Kingdom and in the United States. Now you would think that both would do exactly the same thing, given virtually the same drugs and scientific data. In fact they do not; for a variety of reasons. And one of the basic differences is that in this country patients with essential hypertension are usually begun with a diuretic sort of drug, whereas in England they are usually begun with a beta blocker sort of drug.

Now if one is studying yet a third type of antihypertensive, and one studied it in England, the physicians there and the regulatory bodies would expect that it would be studied with the beta blocker because that's the one it would be most likely be added to. These data would not be nearly as helpful in this country where the majority of physicians would add it to a diuretic.

So sometimes, and I think often companies can anticipate this, it is combinations or patterns of clinical use that differ among countries, even where you might not expect such differences.

Mr. CARNEY. I'll be glad to yield.

Mr. SCHEUER. The whole question of the beta blockers has been of real concern to us, because we feel that the beta blockers have been long delayed, far too long delayed. I'm talking about calcium blockers. And that the regulatory process has been a very costly one in terms of lives.

Let me quote from the last New York Times Sunday magazine section:

> Dr. Donald Harrison, chief of cardiology at Stanford, and president-elect of the American Heart Association, is very enthusiastic about the calcium blockers. "Right now," said Dr. Harrison, "the calcium blockers are the most promising series of drugs in cardiology. I think they will have uses we haven't even dreamed of yet. "What has him and many of his colleagues excited is new evidence that these drugs also work against angina.

And I've been informed that nearly every leading cardiologist in the United States regards this class of drugs as the major advance in the fight against angina pectoris and other heart diseases. Yet your colleague, Marian Finkel, is quoted in the same article, the director of your new drug evaluation section, as saying that "The beta blockers constitute a relatively minor antiarrhythmic drug for abnormal heart beat."

Now it seems to me there's a real problem here: Dr. Finkel downgrades this whole new category of drugs that seem to have excited the entire medical profession. It would seem, since you are overworked and understaffed, that calcium blockers are going to be way down on your priority list, and that the predilection for holding to all the rigidities of the process are going to defeat the efforts of the medical profession and the pharmaceutical industry in get-

ting that whole category of drugs out there in use in the field, saving lives.

Dr. HAYES. May I address that, because it is a very important area. And, as you know, my background is cardiovascular clinical pharmacology, so I have some familiarity with these drugs.

First, just in terms of interpretation, because I think it is that rather than attitude, and Dr. Finkel obviously can say what she will, but in that statement in fact she was addressing the use of an intravenous calcium antagonist for the treatment of dysrhythmics. And I quite share her comment that that is not a very important breakthrough. Indeed, the use of oral forms of calcium antagonists for the treatment of angina pectoris, which is quite a different matter, has all of us, and, I trust, Dr. Finkel, excited in terms of the therapeutic potential. So they are really quite different forms. And I think the statement in that article is quite out of context on the larger issue you and Dr. Harrison, who specifically talked about angina, are raising.

Mr. SCHEUER. I have a right to be confused.

Dr. HAYES. I did not infer that.

Mr. SCHEUER. Don't you have to develop the injectable before you can go to the oral?

Dr. HAYES. Not necessarily. Every drug we have orally in the market is not first developed in an intravenous form. The intravenous form, Congressman, was originally developed for the treatment of specific arrhythmias, as the drug was being tested and tried and otherwise used, and its mechanism in the pharmacological laboratory better understood, the possibility that in certain types of angina its muscle relaxing capabilities might be helpful for angina came to the fore. And that is why the excitement. An intravenous preparation for angina would not make any sense, any more than intravenous nitroglycerin would, or you would be giving yourself a shot for angina 6 or 10 times a day.

So they are quite different situations. The intravenous form was developed for one purpose, the oral form is being looked at for something quite different; and a very important different purpose.

Mr. SCHEUER. I yield back.

Mr. CARNEY. Thank you.

I would just like to ask Dr. Finkel her assessment of the drug that we discussed earlier today with the first witness, Isoprinosine.

What steps has that gone through at the FDA, and where do you see that drug right now?

Dr. FINKEL. Well, the data that were submitted in the new drug application earlier this year were reviewed and found not to be approvable. Actually it was submitted last November, I should say. But they were reviewed and found not to be approvable for effectiveness by the FDA. And we issued a "Not Approvable" letter in July.

The reason we found it not approvable was that our statisticians felt that the statistical analysis upon which the whole basis of effectiveness rested was a faulty one, the analysis done by the firm's consultant. What we're trying to do now is to do different kinds of analyses. In order to do that we have to have access to the registry data.

We have made appointments, or have gotten permission to get the data from all three of the registries that were used for the analysis of the Isoprinosine patients.

Mr. SCHEUER. Dr. Finkel, how do you have a problem of access to that data, when you own the registries, it's your registry?

Dr. FINKEL. We have no problem. Dr. Dyken has agreed to have our statistician go out and look at the data. The head of the Israeli registry said that as soon as she gets back to Israel she will send us the data. And we have an appointment with the keeper of the Lebanon registry for next month.

Mr. CARNEY. I have one further question.

Now, it was rejected on the basis that the FDA felt that its effectiveness was not substantiated by data; is that correct?

Dr. FINKEL. The analysis that was used to establish the effectiveness of Isoprinosine-treated patients in comparison with untreated patients from the registry was felt to be a faulty analysis.

Mr. CARNEY. That's fine. That comes to a philosophical question that I have to continue to pursue. And, by doing that, I'm trying to build a basis.

Have you found any contradictions to the drug because of toxicology, the quality of production, having adverse effects to someone who would consume it any more than as normal drug that has been approved, and it's strictly based on the fact that you don't think the worthiness of the drug's effectiveness to cure some particular ailment is there; is that correct?

Dr. FINKEL. We haven't decided yet, in fact, whether the drug is effective or not. All we have said was that the apparent effectiveness may have been due to a sampling bias that was used for the analysis. The drug appears to be quite safe.

Mr. CARNEY. If the drug is safe, why isn't it marketed, or available, with the knowledge that the FDA says, "We're not sure of its effectiveness," and we can continue to do studies on its effectiveness? It might turn out to be ineffective, it might turn out to be a most important drug in the treatment of certain diseases.

We know that it's not going to have an adverse effect if you take the drug, it's not going to hurt anybody. And if it is not done in a misleading way where we tell them, "Yes, we are 100 percent sure this is going to cure your disease," if it's marketed with the knowledge that its effectiveness has not been certified, then we're moving along, we're making something that very well could be a significant drug available to people now, and we are building a data base to really evaluate its effectiveness. Why don't we do that?

Dr. HAYES. Congressman, it is against the law.

Mr. CARNEY. Why don't we change the law?

Dr. HAYES. That is another discussion. And, as I pointed out earlier in my testimony, looking at the criteria for approval and for effectiveness, and the difference as the law and the courts have defined it concerning substantial and significant evidence, I think it is a very important issue and one that we are addressing. But, in fact, as the law now stands, and as the Federal courts have very clearly said, the FDA is outside, indeed it is breaking the law if it gives permission for the marketing of a drug that has not been shown to be effective.

Mr. CARNEY. Let me put it this way: If I submitted a bill in the House of Representatives to allow you to do that, would the FDA support that? Would we have witnesses come from the FDA that would support that type of activity? Or would you object to it?

Dr. HAYES. I do not think I could give you an answer one way or the other; because if you talk about all drugs, that any drug could be marketed before it had been proven effective, then I think there would be some very real problems.

Mr. CARNEY. Let's narrow it down to compassionate drugs. Would you come in and say "Yes,"—and, again, I'm saying that we know the drug is safe to be consumed by humans, that we have difficulty in making the analysis of its effectiveness. You probably could do it through the Federal Register, but if it's necessary for someone to put a bill in the Congress to get the law changed, would you take a role of being an advocate to that approach to help get drugs out into the market?

Dr. HAYES. I will defer to my counsel, but am persuaded it would require a change of the law before we could use a "significant" or "pending" evidence, or whatever, sort of rule. However, I think that I could generate certainly in my own mind, a good bit of support of conditional approval in special circumstances, such a drug as for a very compassionate condition where there is no alternative drug and where a statement is made in the labeling that in fact we don't know if the drug is effective, that the data at least suggest effectiveness, but have not measured up to the criteria that scientists would otherwise accept.

This has occurred in the law in some other countries. It is sometimes known as breakthrough provisions and the like. You get something on the market rather quickly as long as everybody knows, and the labeling and the advertising is clear, that it has not measured up to the required effectiveness criteria or, perhaps, that long-term safety has not been evaluated. You might need to have a time limit: How long could you continue to market it? What sort of postmarketing surveillance, especially in terms of safety, would you have?

These are very special, but very problematic drug situations under the law as we have it now, as well as in scientific judgment. But I would be very supportive of some way to get these drugs on the market for those who want them.

Mr. CARNEY. I think we've accomplished something in the last 5 minutes. We said, basically—or you said, it's against the law. Well, if it's not going to hurt anyone's health and well-being to take that drug, maybe that law should be changed.

I think we're trying to accomplish that, and I think that's why the chairman has called for these hearings. And I would like to see cooperation with the FDA and with Members of Congress who have a willingness to support an issue like this. I think it would sail through the Congress.

Nobody is talking about allowing a drug to be marketed if the safety of that drug is not 100 percent. Well, I guess there's no such thing as 100 percent certainty; but if the safety of the drug does not meet strict criteria set by the governmental agency, FDA, that's responsible for it. But here we could have a breakthrough that, if it did nothing but to bring some release, some psychological

release to someone who perhaps is terminally ill or under undue stress, pain, we've accomplished that. And, in the meantime we're building data to find out if indeed it's an effective drug.

I'd like to see that pursued, and I would like to see it done immediately. Forget the Commission reports and everything else.

Dr. HAYES. One has to be careful, I think, Congressman, in terms of how broad such provisions are, and what are the safeguards. Because if an effective drug is safe, that is not toxic immediately, does not necessarily mean that it is safe for people to use; because, quite honestly, if there is no efficacy in a drug of any kind, then any safety problem or any risk is too much.

The other problem, of course, that has been discussed in these halls on more than one occasion, and scientists are still attempting to come to grips with, is, how do the physician and the patient handle a situation where a drug is known not to be effective, that there are no data for effectiveness, although perhaps no safety problem, and the patient uses that drug, or demands that drug in lieu of therapy that in fact may be safe and effective? How do you adequately educate people about the alternatives?

Mr. CARNEY. I concur with precisely what you're saying. We're not talking about a drug that is known not to be an effective drug; we are talking about a particular drug whose data have not met criteria set by law.

Dr. HAYES. But it looks good. I agree with you.

Mr. CARNEY. But it looks good.

I don't want to market placebos; I'm not saying that: I don't think we should, for the reasons that you just explained. But if we have a drug that looks like it might have a future, and it looks like it might be an effective drug, why wait? Particularly when you have someone who is terminally ill, or particularly when there is no other alternative. It would be a prudent thing to do.

I think that not only would the drug industry agree with this, but so would the medical industry, and so would the people who are suffering from those types of illnesses. I think right there is something that we can do.

And, as I said before, I don't think it's necessary to sit around and wait for commissions to report, et cetera. I don't say, just put a bill in. I think we need the cooperation of the Government agencies, the Congress, the medical field, academia, and the pharmacological people, all pulled together. And it could be done in the 97th Congress, not the 98th, the 99th or the 100th Congress. And we're not going to be putting anything on the market that would have an adverse effect on anybody.

Mr. SCHEUER. Thank you, Congressman Carney.

Congressman Brown.

Mr. BROWN. May I follow up on that line of questioning briefly, just for my own clarification, because I have a copy of the law in front of me and I'm not sure I understand what it is, particularly.

In your summary on page 17, Doctor, you say the current requirement for substantial evidence of the effectiveness on the basis of adequate, well-controlled clinical trials can delay approval. You suggest a standard of provisional approval on the basis of significant evidence of effectiveness.

Now would that require a change in the law?

Dr. HAYES. It would, sir. The terms in the early part of the paragraph are taken from the law, and decidedly so in this testimony. "Substantial evidence. * * * on the basis of adequate, well-controlled clinical trials" is right out of the legislation.

Very much as Congressman Carney was discussing, what we are suggesting is that a drug might be made available earlier by using the "significant" evidence of effectiveness criteria where there is adequate evidence of safety. But at least I am persuaded by the legal advice I have received that this could not be done short, in terms of court challenge, of change in the legislation.

Mr. BROWN. So you are currently studying this issue. When I state that it means I haven't really looked at it and I don't plan to look at it, but I want to say something to the people who are bugging me about it. [Laughter.]

Is that the situation with you, or do you have a time frame in which you expect to come up with a conclusion on which you will make recommendations for changing the law?

Dr. HAYES. Well, in terms of formal review, it obviously is one of the early issues before our task force on drug approval.

In terms of my own interest I can tell you in all candor that Dr. Crout, Director of the Bureau of Drugs, and I spent almost 2 hours the day before yesterday discussing this exact issue, and I have already asked the General Counsel for some formal opinions on what we can do within the current law, or how the law would have to be changed to let us do what we want, the so-called breakthrough or significant evidence criteria. So I am not putting you off, sir.

Mr. BROWN. All right.

Now going back to the existing law, the requirement is not only for substantial evidence but it's further restricted on the basis of adequate, well-controlled clinical trial. Has that been interpreted through case law to indicate any particular kind of statistical levels that require a certain number of cases or other ways to put restrictions to make it difficult for you to grant approval?

Dr. HAYES. That has occurred. A good bit of it has arisen from the scientific community. Scientists know what a well-controlled clinical trial is, and using the statistics to evaluate data from a clinical trial is the way scientists and clinical investigators and clinical pharmacologists deal all the time. It is not specified in the law.

Mr. BROWN. To be more specific, does a well-controlled clinical trial require a double blind study?

Dr. HAYES. Not necessarily. Sometimes it is not possible. There are different sorts of controls. One of them, for example, is historical control where in fact you use past patients who did not receive the therapy or the treatment currently under investigation, and there is no way, either medically or ethically, to otherwise study it. So, you make a comparison historically.

So, sometimes it is double-blind and sometimes it involves a placebo and sometimes it does not. It may be a comparison of two doses of a particular drug. It really depends upon the state-of-the-art and our medical knowledge and pharmacologic knowledge of that particular drug.

Mr. BROWN. What is the specific sticking point on the Isoprinosine? Can you reveal that?

Dr. FINKEL. The Isoprinosine study used historical control to attempt to establish effectiveness. That is traditionally the most difficult to use because the historically controlled patients must be similar to the treated patients in order to make confirmatory analyses.

The firm's statistician tried to account for the fact that there were differences in the two groups, and that's where our statisticians have a problem with the method by which he tried to do that.

Mr. BROWN. Was it based on the size of the sample?

Dr. FINKEL. It had nothing to do with it. It was just the way it was done.

Mr. BROWN. Well, I would presume that there are substantial difficulties when you have a very small population group that can be studied, as in the case of a disease where perhaps there's only a couple of hundred cases that are all widely different and harder to conduct a study on. Is that true?

Dr. FINKEL. We feel that if we can get the data we need from the registries we'll be able to finish this up.

Mr. BROWN. That's reassuring.

Now you mentioned the registry. My understanding is that the registry is supported by the FDA financially. Is that correct?

Dr. FINKEL. Just the U.S. registry. The others are not.

Mr. BROWN. Yes. Does that mean that the FDA provides the total resources necessary to maintain it or a portion of it, or how does that work?

What is the amount of the grant?

Dr. FINKEL. I have no idea. It's a different bureau that is supporting it. I just don't know.

Mr. MEYER. We would have to insert the specific amount for the record.

Mr. BROWN. My first concern stems from a broader concern about the adequacy of the medical information systems in general, and whether or not there are steps being taken here which could lead to the creation of a more effective system on a broader basis for obtaining the sort of information that's contained in the register. We're bugging the Assistant Secretary for Health of HHS in the same fashion.

I have no further questions.

Mr. SCHEUER. Thank you, Mr. Brown.

Commissioner, isn't it true that two successive advisory committees urged that this drug be approved and found it both safe and effective?

Dr. HAYES. Well, I think what they in fact said was the following:

The first committee in 1980 said that they thought the data was promising that they would like to see an NDA submitted and see positive action on the NDA. You cannot tell somebody to act on something that is not there.

In March, I think it was the 30th, of this year, 1981, the advisory committee met. They reviewed the data and by formal motion stated they believed that the data, such as they had before them, showed that the drug was safe; that it was effective for prolongation of survival; that the data did not show that it was effective for the amelioration of the symptoms.

The chairman, however, before the vote reminded everyone that it was an advisory committee and that it was presumed in its

motion to recommend affirmative action on the drug, that the FDA would audit all of the data by FDA criteria. And in fact that is exactly what we did.

So we really did not do anything other than exactly what the advisory committee presumed we would do. The data became available since that time and the whole analysis then took place. The advisory committee was cognizant of this need and that's why they said they wanted us to look at it and barring any problem—and in fact we have found a problem and are trying very hard to resolve it so the drug can be approved—then they thought it should be approved. So I think we are not outside the advice they gave us.

Mr. SCHEUER. I don't quite understand. "Substantial evidence," the phrase "substantial evidence" has to be a relative phrase. When you have the ability to approve based on "substantial evidence," you have discretion and you have responsibility.

Here you have a drug that's the only ballgame in town. As I understand it, there is no other lifesaving, life-enhancing alternative to isoprinosine for this group of patients. It has been approved by 15 countries around the world.

You heard testimony this morning from Dr. Dyken that two-thirds to three-quarters of his patients live. It's lifesaving. Is that bad? Without this drug all of them would have died.

You heard testimony of the anguish that was felt because with the delay—even when a patient gets that drug if it is delayed beyond the point where attrition of the brain or deterioration of the brain takes place, then the patient will be preserved as a vegetable, not as a fine person with hope, life, talent, that you heard testify this morning in the person of Shelly.

It seems to me that what we have here is a triumph of process and a triumph of bureaucratic rigidity that is absolutely aberrational in its effect of denying the only known drug that has helped a lot of people survive, that is being used all over the world.

And where the inability to obtain that drug means death, and very quick death, how in the world can a compassionate society deny a drug to a person who will die as a cause of not having it where there is no alternative? When the evidence is, it helps most of the people who take it and without it the person will die, how in the world can this agency figure out how many angels are dancing on the head of a pin, let time go by, let patients die while you're trying to decide what "substantial evidence" means?

In this context, "substantial evidence" means that most patients who get it survive and patients who don't get it die. Relative efficacy. What is your answer?

Dr. HAYES. The law requires substantial evidence, sir.

Mr. SCHEUER. But you have the discretion of deciding what "substantial evidence" is.

Dr. HAYES. As well as our "well-controlled clinical trials." The law says "substantial evidence based upon well-controlled clinicial trials."

Mr. SCHEUER. There were clinicial trials here. There are clinical trials available.

Dr. HAYES. There are clinical data, and the analysis of that data by methods used today by the scientific community does not allow

us to approve the drug. Were there a way to use a significant evidence criterion, the drug would be on the market.

Mr. CARNEY. Would the gentleman yield?

Mr. SCHEUER. Surely.

Mr. CARNEY. Doctor, if I'm not mistaken you did say the drug has proven to be life-enhancing.

Dr. HAYES. No, it has not been.

Mr. CARNEY. Didn't you say just before that you had prolongation of survival? Did you not say that?

Dr. HAYES. No, I said that the advisory committee, based upon the data they had before them March 30, 1981, said that it appeared that way to them, but they wanted an FDA audit and analysis of the data to confirm it; that if the FDA analysis, using standards and statistical methods that are accepted by all scientists today, showed that to be true, they thought the drug should be approved.

Believe me, if that were the case the drug would already be approved.

Mr. CARNEY. Thank you for the clarification.

Mr. SCHEUER. Isn't there some way that drug, if it isn't formally approved, can be made available?

Dr. HAYES. It is. It is available to every physician in the country that wants it.

Mr. SCHEUER. It's made available, but the people in California who have to—well, it has to be shipped from California to Chicago and then back to California again. Isn't there something a little bit——

Dr. HAYES. I don't understand what you mean about California.

Mr. SCHEUER. Well, we heard testimony this morning from Shelly's father that the drug is manufactured in California and has to be shipped to Chicago and then shipped back to California. Isn't there some way that that drug can be made available on an experimental basis, patient package inserts and so forth, for this very small constituency of no more than a couple of hundred people in this country? Can't that be made conveniently available to them?

Dr. HAYES. Well, I don't understand the problem that has been drawn, and I will look into it. All I can tell you is that the drug can be made available to any physician who wants it for his or her patients. One does not have to go someplace to get it.

Mr. SCHEUER. Well, apparently they have to go from the West Coast to Chicago to get it.

Dr. HAYES. Well, I will find out. I do not know if this is management or just a snafu in communication. The drug is available to any physician for any patient that he wishes to give it to.

Mr. SCHEUER. You mentioned a number of investigations that are going on and decisions that will be soon made. You're studying this "substantial evidence" rule as mentioned in your testimony.

Do you have any idea when there will be a resolution of that which is fundamental, underlying what we've been discussing?

Dr. HAYES. By "resolution" you mean the recommendations and decisions by the agency? If you mean that, I think they'll be rather quickly forthcoming because it clearly is a very important issue. If indeed legislative change is necessary, I will not speak for how quickly it will become law. That's your side of the table.

Mr. SCHEUER. Right. How soon will you have some recommendations for us?

Dr. HAYES. I think it will probably take a couple of months to do all of the legalities and so on. There has been a lot of work done on this. This is not a new question. The whole idea of "significant evidence" and the "breakthrough" drug is not a new one.

We have, if you will, rekindled the fires under this issue because of the importance that we and, quite frankly, the current Commission feel about it.

Mr. SCHEUER. That's very encouraging. So some time toward the end of the year, November or December?

Dr. HAYES. I would certainly trust so.

Mr. SCHEUER. How about the IRB study which you mentioned in your testimony?

Dr. HAYES. It has already been published in the Federal Register, Mr. Chairman, and I have forgotten the specifics on how many days there are to comment, whether it's 30 or 60. You know, this is a procedural matter. And then we will have to analyze their responses.

We felt this was important because there had been very conflicting notions and suggestions and bits of anecdotal data about the willingness and the ability of IRB to handle the early phases of clinical investigations in the absence of this responsibility by the Food and Drug Administration.

We thought it was important to hear from the IRB's and the hospital administrators and the deans, to what extent they'd be willing to take on this responsibility. There's no good in devising a wonderful scheme and throwing the ball to them if there's nobody there to catch it.

Mr. SCHEUER. You say on page 16, "When completed,* * *" the survey and the analysis, "* * * I will share with you the results * * *" By the end of the year?

Dr. HAYES. I would guess. One has to obviously listen to all of the comment during the publicized comment period, and I would think it would take 30 or 60 days to review, depending upon how many responses we get.

I have sent a letter to these people trying to explain it and encouraging them to respond so that we will have good data, but I can't assure you of that.

Mr. SCHEUER. How about the new drug evaluation process which you discussed on page 14 on the top line there. When do you think that will be completed?

Dr. HAYES. As I think I mentioned later in the testimony, the proposals will be in the Federal Register for NDA's next spring and for the IND process the following fall.

Mr. SCHEUER. Very good.

And when do you think they are going to be actually operational? When do you think they will be actually effective?

Dr. HAYES. Well, once one goes through the necessary comment period and the like, and absent comments that suggest that we made a terrible mistake, or absent a court challenge, they will be effective very shortly after publication.

Some of these changes, quite honestly, Mr. Chairman, that we have discussed I think can probably be put into effect through in-

terpretation of regulation, and as I suggested earlier in my testimony, I'm not going to wait until all the reports are finished, such as the one of our task force, before doing anything. That's when it will all be put together.

Mr. SCHEUER. Very good. That's very encouraging.

Let me ask you about this chart the GAO study.

You will notice that for four of those divisions the approval time has lengthened, and in the most important areas of medicine right now, particularly for middle-class, middle-aged guys like me, the cardiorenal area and the area of oncology.

The GAO also told us this morning that since this report was made there has been a further lengthening of the time for drug approval in those two very most important areas.

Do you have any explanation for this?

Dr. HAYES. Well, I have a partial explanation.

First of all in the oncology area, this really refers not to changes in the approval time for anticancer drugs but, rather, for antiarthritic drugs.

One concern, obviously, and I suppose my own background points me toward this, is the cardiorenal area. I think there are a couple of things that are well known and I believe that these were addressed earlier in discussing this area with the GAO witnesses.

The complexity of cardiorenal drugs has increased tremendously, and that I can say from firsthand experience; not that it hasn't occurred in other areas, but there's no question that the complexity of these drugs, and the disease conditions involved and the ways of treating them. I can tell you from almost bitter personal experience, that one of the hardest things to show is that a particular new drug really decreases the amount of angina when one considers that you can decrease angina by between 30 and 40 percent with a placebo. So it makes it very difficult to show that something really has happened.

Mr. SCHEUER. By just telling people of the new drug and giving them a placebo, they react that way?

Dr. HAYES. If you tell people they feel better, sometimes they do.

Mr. SCHEUER. It's a certain self-fulfilling prophecy at work.

Dr. HAYES. That is correct. The placebo effect is a very powerful one, but you can appreciate that it makes it very difficult to distinguish shades of gray if the standard is a shade of gray, and especially if it's a dark one, in the case of looking like it has intrinsic efficacy.

So I think the testing is very complex. You know, we're talking about drugs used in the treatment of cardiovascular diseases, not those that are rather straightforward and simple. We're talking about preventing a second heart attack. It's very difficult to prove how many people really didn't have a second heart attack over a given period of time because of a drug, when there are so many other factors.

I'm not saying it shouldn't be done. It's terribly exciting. But it makes it more difficult. It means generating data or going back and looking at the data yet another time, and having available experts that really are knowledgeable.

The advisory committee itself does not find it easy evaluating the data on these drugs, and they are the experts in the field.

Mr. CARNEY. If I may, Mr. Chairman?

Mr. SCHEUER. Go ahead.

Mr. CARNEY. Efficacy. When you're talking about a cardiovascular drug or a drug pertaining to all types of heart disease, isn't it rather difficult to determine, because of the length of time involved in doing the studies, prolonging one's life who has cardiovascular disease? They still have not determined whether open heart surgery has any benefit because it takes so long. You'd have to have a generation, a data base, to find out if someone's life was indeed saved after they perhaps suffered from a myocardial infarction or whatever.

Are we that stringent on meeting the efficacy requirement that again we're not getting drugs into the market?

Dr. HAYES. No. On the contrary, the goals for cardiovascular drugs are very much more limited and therefore imminently studyable, even though with difficulty. One does not say with a particular drug that this will increase their life span. That would take a long study and that's what everybody would like. But the much more limited and definable goal is that you will not have a second heart attack within 1 year or 2 years as compared to those who don't have the drug. Either you get it or you don't. You can measure that with an EKG.

Mr. CARNEY. But the efficacy of a drug when you're dealing with heart disease is the fact that it does prolong your life, not necessarily——

Dr. HAYES. That's not true, sir. There are some cardiovascular drugs, as in other areas, that are palliative and are symptomatic. For example, although it has been used for over 200 years for congestive heart failure where, the heart is no longer acting as an efficient pump there is absolutely not one shred of evidence that digitalis it makes the heart any better, that there is any repairative function, that the disease processes, whether it's a valvular disease, or hypertension, are changed one iota.

All it does is, while the heart is still going at all, give it a little extra pharmacologic kick so that the circulation is improved, and the swollen ankles go down and the breathing is easier.

So all cardiovascular drugs do not offer prolongation of life even as a far end point. Not at all. Some of them are palliatives; some are for the relief of symptoms; some are for the relief of signs of those physiologic things that are going on.

Important as it is, I do not think that any drug manufacturer or any scientist would be willing to study a drug only for the prolongation of life; you're talking about 30, 40, or 50 years of study. You study a drug to see whether the arrhythmia goes away; you study a drug to see whether the kidney will put out more urine and more sodium.

Mr. CARNEY. Not being a doctor, perhaps I didn't express myself as clearly as I would want. When I'm talking about prolongation I'm saying "preven." Somebody has cardiovascular disease. OK? And then my drug company is trying to market a drug that might have a significant impact on, you know, cutting down on the incidence of blockage in the thing through plaque or whatever, let's say by reducing the amount of cholesterol in blood levels, triglycerides, and that sort of thing.

To prove the efficacy of that you have to have an awful long study. Am I not correct?

Dr. HAYES. Not necessarily. It is rather simple in fact to show that the drug does or doesn't lower the blood's cholesterol as compared to those individuals who don't take the drugs but eat the same diet. It is the physician's judgments that a lower cholesterol is important in a patient. Or physicians in the aggregate say it's good for patients. We believe, on the best hopefully growing evidence, that it will make a difference in terms of heart attacks or prolongation of life.

What the physician does say is if he can keep the cholesterol down perhaps there will be fewer heart attacks . . . if the evidence eventually supports that. And that's what you study the drug for, to lower the cholesterol. It's a long-term study to see if people live longer.

Mr. CARNEY. OK. You see, this is where I'm confused, and this might get back to the other drug we were talking about before, lowering the cholesterol. We don't know. Does that have an effect on heart disease?

Dr. HAYES. I don't know, but nobody has asked FDA to make that determination.

Mr. CARNEY. What's the effect of lowering cholesterol? Is that a positive effect on one's body?

Dr. HAYES. I don't know. But physicians and patients want drugs that will lower cholesterol because they feel it's important to lower cholesterol.

Mr. CARNEY. But does it have a positive effect on one's body?

Dr. HAYES. Yes, it lowers cholesterol.

Mr. CARNEY. But is that a positive effect? Do we know that? That's the point I'm trying to bring out.

Dr. HAYES. The scientific community at any one time has an opinion about whether that's important or not. I do not think it is incumbent on the FDA to decide that the overall long-term effects of certain drugs are going to be to prolong life, prevent other diseases or the like, or we wouldn't have any drugs on the market at all, and the medical profession wouldn't prescribe any drugs.

Mr. CARNEY. That's why I'm somewhat confused because you're saying in order to get a drug on the market by law it has to have a proven effect. OK?

Dr. HAYES. It has to be effective for that for which it is claimed to be effective.

Mr. CARNEY. OK. And whether that for which it is claimed to be effective has any bearing or positive effect on one's body is not relevant?

Dr. HAYES. Oh, it's very relevant. It's not relevant under our mandate in law. It's extremely relevant as to which drug the companies are interested in studying because if there is no data in the scientific community that lowering cholesterol means anything, then physicians aren't going to prescribe it and companies aren't going to study it and we're not going to be asked about it.

I mean the whole process only moves because there is a need felt in the clinical community. But if the FDA were ever in the position where it had to decide whether lowering cholesterol makes people live longer, the approval time would be a 100 years because it is

going to take that long epidemiologically for the physicians to find out.

Mr. CARNEY. To me there seems to be a conflict there. That's the point that I was trying to bring out. When we have a law that says you have to have a positive effect——

Dr. HAYES. It doesn't say "positive effect." It says that the drug must be shown, with well-controlled clinical trials, to be effective, which means to be effective in doing that for which it is claimed and the way it will be labeled when it will be sold and advertised to physicians.

Now you know you can have claims or effects that lead to another effect that lead to another effect. There is no way that we can respond to that. That's the marketplace, the medical marketplace that involves patients and physicians and the clinical investigators and the pharmaceutical companies and other sponsors.

If physicians feel that the body of evidence that they believe shows that lowering cholesterol prolongs life, decreases symptomotology of angina pectoris, then they will want drugs as well as other modalities for lowering cholesterol. A pharmaceutical firm will develop a drug to meet that clinical demand in the marketplace. They will do the necessary studies and come to the Food and Drug Administration and ask us for approval. Whether or not the physician right that his patient's life is going to be prolonged is not the question; we have no basis for that judgment in law or in science.

What we can show in looking at the data is whether we believe by scientific standards in fact that the drug lowers cholesterol or not, so that when the physician gives the drug at least he knows it does what it says on the label.

Mr. CARNEY. I fully understand precisely what you said, Doctor, and for the record I would like to say that I have a conflict with that because you have to have proof positive that it does a particular thing. That particular thing that the drug does, we don't need proof positive that that's an enhancement to one's life. So to me there's a definite conflict there, and that's something we should be working on.

That's all the questions, Mr. Chairman.

Mr. SCHEUER. Just to sum up on this chart, I know the drug approval process is complicated and it's getting "complicateder and complicateder," as Alice would have said, when you get into these very sophisticated new breakthrough drugs, but that is probably something we're going to have to live with.

I don't suppose there has been any increase in complications in the last couple of years since there has been this deterioration of the process. Do you feel there's a problem there?

Dr. HAYES. I think there's a problem, not only the ones we have already addressed before we got to discussing the efficacy of drugs. The complexity of the drugs, the patients, the sorts of studies that are necessary is only one component, one outside of our control, quite obviously.

Another one is just the workload. The workload of the Cardio-Renal Division, because of the virtual explosion in cardio-renal drugs in the last few years, is unreal. Before I became Commissioner I contributed on the other side so I'm well aware.

A third one which relates to that are resources.

Mr. SCHEUER. Wait a minute. What are you going to do about that problem?

Dr. HAYES. I'll do the best I can to have not only enough people but the right sorts of people that, as I suggested earlier in my testimony, understand these sorts of drugs and the pharmacology and the clinical medicine involved. That is not an easy task.

I'm not suggesting it will all be resolved by throwing people out, but there's no question when the workload increases, you have to to the extent that your budget and other restrictions allow you to put not just people there but the right people.

Mr. SCHEUER. And also you may want to think about whether your system is the right system, because it may be both a combination of people and fine-tuning your system to eliminate unnecessary delays and roadblocks.

Dr. HAYES. We are trying this very hard, and I think you will see this addressed very straightforwardly in the NDA rewrite. Some suggested changes in the regulations that we are looking at, in fact, are more than fine-tuning. It's my suggestion, in many cases perhaps to do away with case summaries and use something to remove these burdens, and I think you will see a face-on confrontation by FDA with these problems.

Mr. SCHEUER. We're looking foward to that very much.

Let me ask you: On your task force it's wholly internal in terms of the personnel? It's only FDA? I was curious why nobody contemplated reaching out and perhaps getting some top pharmacologists from the pharmaceutical industry, perhaps deans of schools of pharmacology in our medical schools, perhaps some pharmacological experts like yourself from the medical community, from the county and State medical associations, from the AMA.

It seems to me there might have been some advantages to broadening the membership.

Dr. HAYES. I'll tell you why I think that's a terribly relevant point and one that we obviously addressed.

The reason everyone is, if you will, from inside or from the Department is the following: There are other groups, most especially the Commission which you were instrumental in forming, that has that sort of formal decisionmaking, recommending participation. This particular task force, listening to what that Commission says as well as a variety of other sources including our own generated data, has really got to make the decision.

The FDA is the one that has to decide what we're going to do, what the regulations will or will not be, or how we're going to interpret them. Other people can't make that decision for us.

The outreach of this task force, however, is rather large. At each one of our meetings, the first half, before the executive session, is devoted to ad hoc representatives who come in to discuss various issues on points that we would like to ask their help, or where they would like to come in de novo and present information to us.

And indeed, Dr. McMahon spent an hour with us at our very first meeting, as you perhaps know. So the outreach is going to be everywhere.

But in terms of the decisionmaking, it is the Commissioner with his people who must make the decision.

Mr. SCHEUER. Very good. You are getting that outreach informally and I'm very much encouraged that you're going to be working closely with our commission and that you have some top people working with you. We appreciate that, and I think it is going to be very valuable.

I'm going to have to leave here in 6 minutes. We have a rollcall vote on right now.

Can you tell us of any legislative changes that you think we ought to be contemplating? You can give us some ideas if you wish to now, or you can submit that in writing.

Dr. HAYES. Well, I can't give you the answers now because as perhaps I implied earlier, there are some areas, the one we discussed most recently about the breakthrough drug provision, or the significant evidence criterion, and some others where in fact we may need legislative relief, some changes in the law.

I'm not prepared to address that until I know what my goals are, what I want to accomplish. Then if we feel that recommendations are appropriate we will, through the Secretary, bring them to the Congress and ask that we be given that relief.

Mr. SCHEUER. Very good. That's perfectly reasonable.

On your foreign studies which you discussed before, of course they would have to be made on the basis of validity and the quality of data. Otherwise they wouldn't be equivalent to American studies. But I am concerned. Once you have established the validity and the quality of the data, why we cannot—oh, let me ask you this:

You mentioned some countries that don't open up their case studies and so forth. Which countries are they?

Dr. HAYES. Well, there are some countries in Western Europe as well as elsewhere that investigators will not prepare case report forms. They will tell you what they found, but they will not provide information objectively.

Mr. SCHEUER. Can you tell us what countries they are?

Dr. HAYES. Well, I think, because I learned that before I became Commissioner, under another aegis, it would be unethical for me to publicly mention the countries. I'll be happy to share them with you elsewhere.

Mr. SCHEUER. All right.

Dr. HAYES. Because I'm afraid the individuals could be identified, and I think that would be inappropriate.

But it does occur, unfortunately. It is not universal. There are some superb individuals; some of the best clinical investigators exist outside of the United States. The question is the uniformity or the ability to be sure that the investigation, the facilities in terms of the hospitals or the clinics or the offices, meet the standards that I think we would all agree are appropriate for this sort of research.

Mr. SCHEUER. That's a legitimate question. I will perhaps talk privately about it.

How about the many developed countries where we do have access? England? France? Germany? Switzerland? Japan? The rest of them? When they develop a drug there with substantially the same kind of populations that we have here and they're tested and available to us and it meets our standards of validity and quality,

why do we have to waste several years time perhaps duplicating those studies here? Why can't we accept those studies?

Why can't we accept those as the only studies if they are up to our standards of quality and we'd only be duplicating?

What's wrong, as a judgmental manner, in accepting those studies that are adequate as the only needed and only appropriate studies?

Dr. HAYES. I can't answer that. I think that's a very legitimate question as long as all the other concerns that I earlier and you have just now suggested exist, in terms of differences amongst the countries and the like. I think it's a very legitimate question and, indeed, it's a first issue before our task force, that is, the degree of acceptance of foreign data and whether some changes there, in fact, are indicated.

So it probably has No. 1 priority right now with the task force.

Mr. SCHEUER. Excellent.

One last question:

Do you believe that we ought to enhance the effectiveness of the advisory councils? For example, should they be given—should their decisions or recommendations be given presumptive evidence? Should we legislate, for example, that FDA has 60 or 90 days after the advisory council recommendations, and if they don't come up with evidence that they are negligent, or there's a conflict of interest or fraud? They forgot to include basic information or they didn't add up the figures right, and in the absence of compelling evidence, that there would be a rebuttable presumption that the advisory council reports would stick and after 60 or 90 days they would be accepted?

Dr. HAYES. There are a couple of difficulties with that. The first thing is that we very rarely disagree with our advisory committees.

Mr. SCHEUER. Yes, but there are long lapses of time. That's the problem.

Dr. HAYES. The problem is, you said, the advisory committtee's decision becoming the final one.

Mr. SCHEUER. After a specific period of time.

Dr. HAYES. But if you did that, one of the problems is that then you would have difficulty with the advisory committee members because they would be held accountable for a policy decision. I think there are other ways to improve the managerial efficiency of going from committee decision to a final FDA decision.

Mr. SCHEUER. Commissioner, I'm being held accountable for catching a rollcall vote so I've really got to go. I want to thank you very much for your cooperation, for your forthcoming testimony. We'll be working with you. We'll be performing our legitimate oversight function. We'll be looking for specific, identifiable problems.

I'm a candidate for cardio-renal treatment and oncological treatment, being in my aging, declining years, as many Members of Congress are. So I'll be looking with very special interest on improvements in these statistics.

Thank you again for coming. We'll have some additional written questions for you, and in the next few months we'll impose on your patience to return.

Thank you very much.

[Whereupon, at 12:58 p.m., the meeting of the subcommittee was adjourned.]

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